

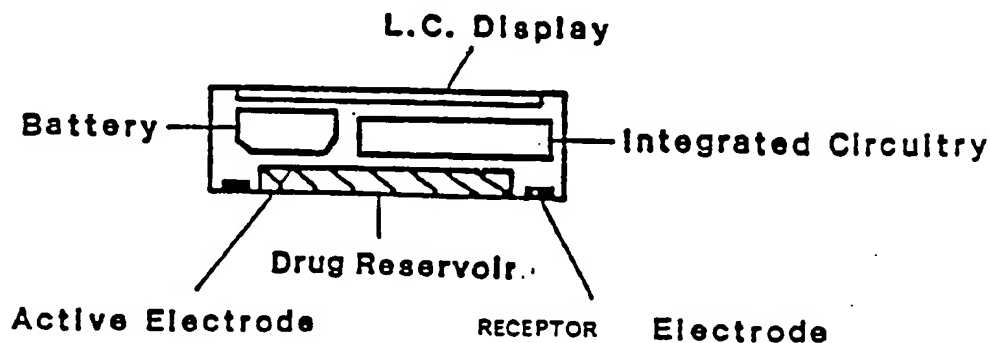


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61N 1/30	A1	(11) International Publication Number: WO 93/03790 (43) International Publication Date: 4 March 1993 (04.03.93)
(21) International Application Number: PCT/US92/07221 (22) International Filing Date: 26 August 1992 (26.08.92) (30) Priority data: 749,928 26 August 1991 (26.08.91) US (71) Applicant: RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY [US/US]; Old Queens Building, Somerset And George Streets, New Brunswick, NJ 08903 (US). (72) Inventors: CHIEN, Yie, W. ; 5 West Lake Court, North Brunswick, NJ 08902 (US). SHI, Wei-Min ; 81 Lincoln Avenue, Piscataway, NJ 08854 (US).	(74) Agent: SINN, Leroy, G.; P.O. Box 559, Oldwick, NJ 08858 (US). (81) Designated States: AU, CA, DK, ES, FI, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: IONTOTHERAPEUTIC DEVICE AND PROCESS

TRANSDERMAL PERIODIC IONTO-THERAPEUTIC SYSTEM (TPIS)



(57) Abstract

This invention relates to a portable, lightweight iontotherapeutic device for regulated transdermal systemic administration of ionizable pharmaceutical compounds. The device has a preprogrammable control element which controls the iontotherapeutic administration in accordance with a prescription and other instructions entered into the control element by interface with a computer system and which can communicate data on the iontotherapy by interface with a computer system. It also provides an iontotherapeutic process for automated transdermal administration of ionized pharmaceuticals by use of the device. Also provided is a novel battery belt adaptable for use with the device.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MN	Mongolia
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Faso	GN	Guinea	NO	Norway
BG	Bulgaria	GR	Greece	NZ	New Zealand
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	PT	Portugal
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovak Republic
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CS	Czechoslovakia	LU	Luxembourg	SU	Soviet Union
CZ	Czech Republic	MC	Monaco	TD	Chad
DE	Germany	MG	Madagascar	TG	Togo
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain			US	United States of America

5

IONTOTHERAPEUTIC DEVICE AND PROCESS

10

CROSS-REFERENCE TO RELATED APPLICATION

15

This application is a continuation-in-part of U.S. Application Serial No. 07/587,406 filed September 25, 1990 and of U.S. Application Serial No. 07/046,984, filed May 5, 1987, now U.S. Patent No. 5,042,975, which was a continuation-in-part of U.S. Application Serial No. 890,702 filed July 25, 1986, now abandoned.

20

25

TECHNICAL FIELD

30

This invention relates to development of an iontotherapeutic device for regulated transdermal systemic administration of ionizable pharmaceuticals (including ionizable biopharmaceuticals) and a novel battery device usable as an element of said device.

35

40

It also provides an iontotherapeutic process for transdermal administration of ionizable pharmaceuticals, particularly those which are otherwise transdermally absorbed to a small degree or not at all. The invention also relates to a polymeric unit dose in which an ionized pharmaceutical is dispersed. The unit dose is adapted to be assembled as a part of either the anode or the cathode, depending upon whether the ionized pharmaceutical is cationic or anionic, so that the ionized pharmaceutical will be delivered transdermally and then be absorbed systemically when the iontotherapeutic device is in operation.

45

50

55

5

BACKGROUND ART

10 Many pharmaceuticals are required to be administered to
patients by injection. A notable example is insulin, which
cannot be administered orally to be effective in lowering
15 the elevated blood sugar levels, which are too high in
diabetics (i.e., > 126 mg/dL). Other pharmaceuticals may be
administered orally, but in some cases, there is inefficient
20 absorption into the bloodstream to permit the pharmaceu-
ticals to achieve their intended therapy. Also, with regard
to oral administration, many orally administered pharmaceu-
25 ticals undergo a high degree of destruction by the hepato-
gastrointestinal first-pass metabolism. Often the metabo-
lites of the first-pass metabolism cause unwanted biological
30 activity or toxicity. In oral administration, there are
variables which cause undesirable variations in the extent
35 of gastrointestinal absorption from subject to subject,
especially in the case of some pharmaceuticals; and there
40 are also associated problems of uneven blood levels result-
ing from an initial large absorption with attendant un-
desirable side effects or toxicities, and subsequent blood
45 levels which are less than therapeutically optimal.

Recently there has been an increasing interest in
50 transdermal delivery. However, it is desired that transder-
mal absorption of a number of pharmaceuticals, particularly
the macromolecular drugs such as insulin and cationic drugs
55 like propranolol HCl, be improved.

5

10

15

The hazard and discomfort of administration of pharmaceuticals by injection, especially if therapy is required on a frequent basis, such as the subcutaneous injection of insulin for diabetes therapy, which is required daily, are universally known. There has long been a desire to avoid the necessity of therapy by injection.

20

25

30

35

40

45

Investigations have been carried out to explore the possibility of delivering certain therapeutic agents topically by use of a direct current (DC) iontophoresis. For example, it has been found that fluoride ions can be assimilated into the structure of a tooth with the aid of DC iontophoresis. Also, localized "seating" has been caused by delivering to the skin a sweat-inducing compound, such as pilocarpine, using a direct current. The induced sweat is then assayed using an electrode to determine its chloride ion concentration for diagnosis purposes. A low chloride content in the sweat indicates that a patient may be suffering from cystic fibrosis. Application of a DC iontophoresis can be uncomfortable particularly when the level of applied current is at a high level, in the case of certain pharmaceuticals, in order to achieve a systemic therapeutic level.

50

55

It is highly desired to provide improved iontotherapeutic devices and processes and unit dose forms for use therein and to provide further thereby therapeutic levels of systemically-effective pharmaceuticals efficiently with a physiologically-acceptable low electric current.

5

SUMMARY OF THE INVENTION

10

15

20

25

30

35

40

45

50

55

A process has been found for administering transdermally a systemically effective amount of an ionizable pharmaceutical in sterile aqueous solution using an iontotherapeutic device such as provided by this invention. The ionized pharmaceutical solution can be contained in a unit dose form such as disposable polymeric matrix unit dose form in which a dosage amount of an ionized pharmaceutical solution (pH desirably at least about 1.0, 1.5 or about 2 pH units above or below the pKa or isoelectric pH of the ionizable pharmaceutical) is intermixed with a polymer which is characterized by being compatible with the pharmaceutical as well as the skin, hydrophilic, and capable of releasing the pharmaceutical for iontotherapeutic transdermal absorption. The unit dose form can also comprise a sterile solution of the ionized pharmaceutical contained within a closed reservoir unit dose form having a drug-releasing microporous membrane surface. The unit dose forms are assembled with a pharmaceutical reservoir electrode and are further adapted to permit the dissolved, ionized pharmaceutical to be delivered iontophoretically to the skin of the subject treated and to provide iontotherapeutic transdermal absorption of a systemically effective amount of the pharmaceutical. The unit dose forms are maintained covered to retain sterility until the desired time of iontotherapeutic administration. A pharmaceutical reservoir electrode which will receive such a unit dose form is used as a part of the

5

10

15

20

25

30

35

40

45

50

55

iontotherapeutic device, such as provided by this invention, which is used to carry out the iontotherapeutic delivery and transdermal absorption of the ionized pharmaceutical. The pharmaceutical reservoir electrode is either a cathode or an anode depending upon whether the pharmaceutical is in anionic or cationic form, respectively. The iontotherapeutic device provides, in the process, an iontotherapeutically effective and physiologically acceptable pulse current with a specific waveform having an amplitude such as up to about 10mA based on a reservoir electrode skin-contacting area of about 5 cm² and an effective frequency of at least about 10 Hz up to about 50 KHz until the subject treated has received a pharmacologically-effective systemic dosage of the ionized pharmaceutical.

The pharmaceutical administered by this invention can be selected from pharmaceuticals which ordinarily are not transdermally absorbed through intact skin in an effective dosage amount, such pharmaceuticals including but not limited to insulins, vasopressin, heparin, growth hormones, glucagon, oxytocin, and other macromolecular drugs as well as a number of others which can be provided in ionized form. A number of compounds which are naturally-occurring in humans, or variants thereof, and which often are peptide in nature, are also included within this pharmaceutical group, many of which can be produced identically or as a related

5 compound using DNA recombinant or other biological techniques.

10 Also provided by the invention is a novel iontotherapeutic device capable of transdermally administering a systemically effective amount of an ionized pharmaceutical.
15 The device is a lightweight, portable transdermal periodic iontotherapeutic device for transdermal administration of a
20 systemically-effective amount of an ionized pharmaceutical, which is adapted to be worn by a subject being iontotherapeutically treated, comprising

25 1) a DC power supply capable of providing an iontotherapeutically effective and physiologically acceptable DC
30 current in the range up to about 10mA;

2) a periodic waveform generator electrically connected to
35 the DC power supply and having integrated circuitry capable of providing a) a periodic waveform in the square, triangular, sinusoidal, trapezoidal, or other
40 acceptable geometric form or combination thereof; b) an on/off ratio of 1/50 to 10/1; and c) a repetition frequency from about 10 Hz to about 50 KHz;

45 3) an output circuit electrically connected to said waveform generator which a) can provide a periodic DC current in a pre-selected waveform of said forms; b) monitors current intensity delivered; c) adjusts and maintains the current intensity within predetermined maximum and minimum levels and d) delivers the current to a
50
55

5

reservoir electrode for iontopherapeutic transdermal administration of said ionized pharmaceutical;

10

4) a pharmaceutical reservoir electrode which can be pre-selected to be either the cathode or the anode depending upon whether the ionized pharmaceutical is anionic or cationic; said electrode having a receptacle adapted to receive a unit dose of said ionized pharmaceutical in which said ionized pharmaceutical is in aqueous solution at a pH at least 1.0 pH unit below or above the isoelectric point or pKa point of said ionized pharmaceutical ; said electrode with said received unit dose adapted to be placed in electrical contact with the intact skin to be treated iontopherapeutically; said electrode having a terminal to receive and to transmit through said unit dose the said periodic DC current and said unit dose adapted to be in electrical contact with said terminal;

40

5) receptor electrode adapted to be in electrical contact with the intact skin to be treated and forming with said pharmaceutical reservoir electrode a combination of anode and cathode electrodes;

50

said electrodes electrically connected to said output circuit and providing when placed upon the skin of a subject being treated a current path through the intervening tissue of the subject being treated; and

55

5

6) a preprogramable control element electrically integrated within said device to preprogram and to control
10 said iontotherapeutic administration on an automated basis as in accordance with a physician's prescription entered into the control element, without interaction
15 of a subject being treated with the device for said administration except to permit said subject to stop operation of the device as in the event of an emergency.

25

The device will ordinarily have a terminal by which the transdermal administration carried on by the device can be
30 monitored using a computer system and a connecting line to connect the device and the computer system or by which a prescription for administration of a pharmaceutical by the
35 device can be entered into the programmable control element by use of a computer system and a connecting line to connect the control element with the computer system.

40

Further, the device desirably has one or more additional terminals by which the control element can be connected
45 by a connecting line with a sensor to sense a skin condition or with a separate sensor to sense a level of an entity in the body (which correlates with a need for administration of the pharmaceutical), the sensor(s) held in
50 intimate contact with the subject's body and signals said control element on need for administration or skin condi-

55

5 tion. For example, in insulin iontotherapy, the signal can transmit the nature of need for insulin administration.

10 Further, the invention provides a process for administering an ionized pharmaceutical by use of the above defined device and carrying out the following steps:

- 15 1) entering a prescription or other instructions into the control element of said device using a computer system;
- 20 2) assembling a dosage unit containing a pharmaceutically acceptable aqueous solution of said peptide into a receptacle of a reservoir electrode of a transdermal
- 25 periodic iontotherapeutic system, which electrode is a cathode or anode depending upon whether such ionized peptide is anionic or cationic, said solution having a
- 30 pH at least about 1.0 pH unit below or above the isoelectric point of said peptide;
- 35 3) placing the cathode and anode electrodes of said transdermal periodic iontotherapeutic system in electrical
- 40 contact with the intact skin to be treated; and
- 45 4) applying an iontotherapeutically effective, periodic DC current of up to about 10mA based on a reservoir electrode/skin-contacting area of about 5 cm² using a) a
- 50 periodic waveform in the square, triangular, sinusoidal, trapezoidal, or other acceptable geometric
- 55 form, or combinations thereof, b) a physiologically acceptable repetition frequency of at least about 10

5 Hz, and c) an on/off ratio of from 1/50 to 10/1; said
process providing a systemically effective absorption
10 of said peptide pharmaceutical from said solution at a
rate of at least 500 percent from that provided by
passive diffusion transdermal absorption from said
15 solution during an administration time of at least 2
hours.

20 The above defined process desirably is carried out
wherein a sensor is held in intimate contact with the body
25 of subject being treated such as in intimate contact with
the skin of the person being treated and said sensor trans-
mits one or more signals to the control element of the
30 device such as a physiological factor of the subject being
treated which correlates with the pharmaceutical administra-
35 tion carried out by the device or a skin condition which
relates to the transdermal administration.

40 BRIEF DESCRIPTION OF THE DRAWINGS

45 FIG. 1 is a diagram portraying a device of the inven-
tion in operation to effect iontotherapeutic transdermal
absorption of an ionized pharmaceutical and its uptake into
50 the bloodstream of the subject treated.

FIG. 2 is a block diagram of a transdermal periodic
iontotherapeutic device parent application Serial No.
55 07/046,984.

5

FIG. 3 is a block diagram of a transdermal periodic iontotherapeutic device coming within the invention.

10

FIG. 4 is a detailed circuit diagram for the Square-Wave Generator shown in FIGS. 2 and 3.

15

FIG. 5 is a detailed circuit diagram for the Trapezoidal-Triangular Wave Generator shown in FIGS. 2 and 3.

20

FIG. 6 is a detailed circuit diagram for the Sinusoidal Signal Generator shown in FIGS. 2 and 3.

25

FIG. 7 is a detailed circuit diagram for the Output Circuit shown in FIGS. 2 and 3.

30

FIG. 8 is a block diagram of a wristwatch-type miniaturized periodic iontotherapeutic device coming within the invention, in which the drug reservoir electrode is positioned away from the main portion of iontotherapeutic device.

35

40

FIG. 9A and 9B are diagrams illustrating a wristwatch-type miniaturized transdermal periodic iontotherapeutic system with the drug reservoir electrode positioned directly in the lower portion of the iontotherapeutic device and with multifunctional programmability.

45

FIG. 10 is a block diagram of a portable transdermal periodic iontotherapeutic device.

50

FIG. 11 and 11A are detailed circuit diagrams of the device shown in FIG. 10.

55

FIG. 12 is a detailed circuit diagram showing an electronic timer element which can be used to control the iontotherapeutic administration.

5

FIG. 13 is a schematic diagram of a wrist-type ionto-
therapeutic device coming within the invention showing a
10 belt-type battery power supply and a sensor for blood sugar
monitoring.

15 FIG. 14 is a schematic diagram showing an iontothera-
peutic device of this invention in interface with a computer
system through a connecting line (e.g., interface cable/
20 telephone line).

FIG. 15 is a schematic diagram of an iontotherapeutic
25 device of this invention using a belt or band to attach to
the subject being treated.

30 FIG. 16 is a graph comparing the effects of periodic
wave mode and DC mode on the transdermal absorption of insu-
lin and on the reduction of blood glucose level (B.G.L.) in
35 the diabetic hairless rats.

FIG. 17 is a graph showing the time course for the
40 reduction in the blood glucose level (B.G.L.) in the dia-
betic hairless rates as the result of transdermal delivery
of insulin from a pharmaceutical reservoir electrode con-
45 taining 250 IU of insulin at pH 3.6 by transdermal periodic
iontotherapeutic system with square waveform mode (1mA;
on/off = 1/1; frequency = 2 KHz) for 40 min.

50

FIG. 18 is a graph showing the effect of the frequency
generated by the transdermal periodic iontotherapeutic sys-
55 tem on the reduction in the blood glucose level (B.G.L.) in
the diabetic hairless rates using insulin.

5

10

FIG. 19 is a graph showing the effect of the on/off ratio in the transdermal periodic iontotherapeutic system on the reduction in the blood sugar level (B.G.L.) in the diabetic hairless rats using insulin.

15

20

FIG. 20 is a graph showing the effect of the treatment duration by the transdermal periodic iontotherapeutic system with drug reservoir electrode at pH 3.6, on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rats using insulin.

25

30

FIG. 21 is a graph showing the effect of the treatment duration by the transdermal periodic iontotherapeutic system, with drug reservoir electrode at pH 7.1, on the reduction in the blood glucose level (B.G.L.) in the diabetic hairless rats using insulin.

35

40

FIG. 22 is a graph showing permeation of vasopressin facilitated by the transdermal periodic iontotherapeutic system compared to passive diffusion of a vasopressin solution at pH 5.0 through hairless rat skin.

45

FIG. 23A is a graph showing permeation rate of insulin solution at pH 7.1 through hairless rat skin using no iontotherapy as compared to permeation rate shown in FIG. 21B when using iontotherapy (TIDD).

50

55

FIG. 24 is a series of graphs showing the comparative effects of the change in waveform in lowering blood glucose level (B.G.L.) in diabetic hairless rats using transdermal periodic iontotherapeutic system using insulin solution at pH 3.68.

5

10

FIG. 25A is a graph showing lowering of blood sugar level (B.G.L.) of hairless rats using transdermal periodic iontotherapeutic system on Day 1 using insulin solution at pH 3.68.

15

20

25

FIG. 25B is a graph showing further lowering of the blood sugar levels of the same rats on Day 3 using transdermal periodic iontotherapeutic system without further administration of insulin, indicating that the insulin delivered transdermally on Day 1 is stored in the skin tissues and can be activated to become available for absorption into systemic circulation on Day 3 by TPIS.

30

35

40

FIG. 26A is a pair of comparative graphs showing plasma immunoreactive insulin levels in diabetic rabbits after administration of insulin solution (pH 7.1) using transdermal periodic iontotherapeutic system (TPIS) compared with corresponding levels in diabetic rabbits using subcutaneous administration (SC). "SZ injection" indicates injections to render rabbits diabetic.

45

50

FIG. 26B is a pair of comparative graphs corresponding to those of FIG. 24A showing the respective reduction of blood glucose levels (B.G.L.). The data show that blood glucose levels can be controlled at a highly constant level so as not to fall substantially, if at all, below normal levels by TPIS.

55

5

10

15

20

FIG. 27A is a pair of comparative graphs showing the increase in plasma insulin concentration after administration of insulin solution (pH 7.10) using transdermal periodic iontotherapeutic system (TPIS) compared to using transdermal iontotherapeutic system (TIDD) in which 4X current intensity and 2X administration times are used. TPIS administration shows more rapid attainment of increased plasma insulin concentrations.

25

30

35

FIG. 27B is a pair of comparative graphs corresponding to those of FIG. 25A showing the attained lowering of blood glucose levels (B.G.L.). The data show a near instantaneous reduction of blood glucose level from the hyperglycemic level in the diabetic controls using transdermal periodic iontotherapeutic system (TPIS) whereas the reduction using transdermal iontotherapeutic system (TIDD) is lower than the normoglycemic level.

40

45

50

FIG. 28 is a pair of comparative graphs showing a desired reduction in urine output as indicated by urine osmolarity measurement in anesthetized rabbits using transdermal periodic iontotherapeutic system to administer vasopressin solution (pH 5.0). The corresponding graph shows that TPIS is more effective in reducing urine output than TIDD.

55

FIG. 29 is a graph showing vasopressin permeation rate enhancement when the ionic strength of the vasopressin solution used in TPIS is decreased.

5 FIG. 30 is a graph showing enhancement of skin permea-
tion of vasopressin using TPIS with a short skin permeation
10 lag time. The graph also shows reversibility of skin per-
meation within 2 hours after ceasing TPIS treatment and
again enhancement of skin permeation after reinstituting
15 TPIS.

20 DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED
 EMBODIMENTS

25 FIG. 1 is a diagram portraying a device of the inven-
tion in operation to deliver iontotherapeutically an ionized
pharmaceutical and its uptake into the bloodstream of the
30 subject being treated. The figure shows the iontotherapeu-
tic device in electrical contact with the skin.

35 It also shows the pharmaceutical reservoir electrode in
contact with the skin as well as the other electrode, which
is referred to as the receptor electrode. The electrodes
40 are in contact with the uppermost skin barrier, called
stratum corneum. The pharmaceutical is transmitted through
45 the stratum corneum and flows into the dermo-epidermal
layer. The stratum corneum is the principal absorption rate
limiting barrier. The first portion of the dermis layer is
50 referred to as the papillary layer, which contains a capil-
lary network of the vascular system. The capillary network
takes up the transdermally absorbed pharmaceutical and the
55 uptaken pharmaceutical is shown to flow from the capillary
network into the main portion of the vascular system.

FIG. 2 is a block diagram of a transdermal periodic iontotherapeutic device coming within the invention in which the power supply is derived either from the conversion of the alternate current (AC) from a 120 V-mains (or other available AC mains) into direct current or from a suitable battery. The power is turned on manually by a switch or automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. The multifunction generator is assembled with a power supply, to delivery direct current with periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically-effective waveform can be selected manually or preprogrammed through a switch (K_1), and the frequency of the output waveform can be adjusted in the range of 10 Hz - 50 KHz. The output circuit then provides a physiologically acceptable current, for example, ranging up to 10 mA, to the pharmaceutical reservoir electrode which contains the ionized pharmaceutical to be delivered transdermally, and a receptor electrode in series. When desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

5

FIG. 3 is a block diagram of an iontotherapeutic device of this invention. It consists of the following elements:
10 a microprocessor, a multiple waveform generator, a waveform selector, an output circuit, a sensor signal processor, a display unit, a power supply with indicator, a reservoir
15 electrode, and a receptor electrode.

The microprocessor is the center of the device. It has
20 the following functions:

- a. receiving and processing the physiological signal(s)
25 from the sensor element;
- b. communicating with a computer system via an interface
cable;
- 30 c. receiving and exercising commands from the computer
system;
- 35 d. storing data and transmitting data to the computer
system;
- e. controlling operation parameters of the multiple wave-
40 form generator, such as frequency and duty cycle of
generated waveforms;
- 45 f. selecting the input waveform of the output circuit;
- g. controlling the operation parameters of the output
circuit, such as output current amplitude and treatment
50 cycle;
- h. monitoring the load impedance of the device and alert-
55 ing the user of improper operation conditions.

5

10

15

20

25

The microprocessor is made using a commercial single chip microcontroller with necessary expanded memory capacity, additional input/output ports and signal converters. A preferred microcontroller is 80C552 single chip microcontroller made by Signetics, a subsidiary of Philips Components. This microcontroller is very powerful and meets the requirements of the current application. It has the following important features: 16 MHz speed, 8K ROM and 256K RAM memory, 4 watchdog timer-counters, 6 I/O ports and 8 channel 12 bit A/D, UART and I²C interfaces, and 6 external interrupts.

30

35

The multiple waveform generator provides pulse-mode signals of desired waveforms. It can be realized by using the circuitry shown in FIG. 6. It can also be made by using a commercial integrated circuit ICL8038 made by Motorola Corporation.

40

The waveform selector can be made using a commercial electronic analog switch, such as AD7510 made by Analog Devices.

45

The output circuit can be made by using the circuit design shown in FIG. 7 or using a three-pin constant current regulator LM334 made by National Semiconductor Corporation.

50

55

The function of the sensor signal processor is to further condition the physiological signals, such as blood glucose level signals. It provides necessary function, such as amplification and filtering of the signals. The conditioned signals will be sent to the analog/digital converter

5

of the microprocessor. They will be used for close-loop control of iontotherapeutic treatment.

10

The power supply unit consists of battery elements connected in series. The batteries can be either regular ones or rechargeable ones. A low-batter indicator will be used to signal the low battery condition.

15

20

FIG. 4 is a detailed circuit diagram for the square wave generator shown in FIG. 2. It employs a microchip 555 timer. The frequency (F) of the square wave is:

25

$$F = \frac{1}{t_1 + t_2} \quad \begin{aligned} t_1 &= 0.693 (P_1 + P_2) C \\ t_2 &= 0.693 P_1 C \end{aligned}$$

30

35

40

where P's are potentiometers, C is a capacitor, and D's are diodes. During the operation, the capacitor C is charged through the potentiometer P₁ and P₂ and the diode D for t₁ seconds and discharged through potentiometer P₁ and diode D₂ for t₂ seconds. Other circuits can be used in place thereof.

45

50

55

FIG. 5 is a detailed circuit diagram for the triangular-trapezoidal waveform generator shown in FIG. 2. It consists of an integrator (A) and a regenerative comparator (B) connected in a positive feedback loop. Precise triangular waves are formed by integration of the square wave which is fed back from the output of the comparator to the input of the integrator. The frequency (F) of the triangular wave is:

5

$$F = \frac{1}{t_1 + t_2} \left(\frac{t^1 = V_{o+} - V_{o-}}{R_2} R^1 \frac{V_{o+}}{C (P_2 a + P_3 b)} + \frac{t^1 = V_{o+} - V_{o-}}{R_2} R^1 \frac{-V_{o-}}{C (P_2 a + P_3 b)} \right)$$

15

where V_{o+} and V_{o-} are the higher and lower trip points of the comparator, respectively. Resistors R_1 and R_2 control the comparator trip points. Capacitor C is the integration capacitor. Potentiometer P_1 provides adjustment of the triangular wave offset. Potentiometers P_2 and P_3 adjust frequency and symmetry, respectively.

The third op-amp circuit (C) acts as a damper. It produces a trapezoidal wave with the same frequency as the triangular wave. Potentiometer P_4 sets the clamping level. Other circuits can be used in place thereof.

FIG. 6 is a detailed circuit diagram for the sinusoidal signal generator shown in FIG. 2. The circuit of the generator uses two amplifiers: one (A) acts as a non-inverting integrator, and other (B) acts as an inverting integrator. They are connected in cascade to form a feedback loop. The frequency (F) of the sinusoidal signal is determined by:

$$F = \frac{1}{2 CP}$$

55

5

C's and P's are integration capacitors and the variable resistors, respectively. Resistor R_1 is a feedback resistor. Capacitor C_1 is used to prevent high-frequency oscillations. Other circuits can be used in place thereof.

10

15

20

25

30

FIG. 7 is a detailed circuit diagram for the Output Circuit shown in FIG. 2. The desired waveform is selected manually or automatically from the 3 generators through a switch (K_1) and sent to the inverting amplifier, from which the signal then goes to the output stage of two transistors. The output current (dose current) is adjusted by a potentiometer (P), as monitored by a current meter (A), and is delivered to the drug reservoir electrode (B). Other circuits can be used in place thereof.

35

40

45

50

55

FIG. 8 is a diagram illustrating the wristwatch-type miniaturized transdermal periodic iontotherapeutic system with multifunction programmability. It is designed to have one or more nuclear batteries and two pieces of microchips: one for the purpose of generating different waveforms, as outlined in FIGS. 4-6, and the other is for the purpose of controlling and to display the output current. The nuclear batteries provide the energy needed for long-term operation. For instance, the programmability may include selection of DC alone or in combination with a periodic waveform, a dose current for a particularly designated time period. In certain applications, it may be advantageous in operating the devices of this invention to have the periodic current wave-

5 form remaining at some constant DC level during the off
cycle. In this design of iontotherapeutic device, the drug
10 reservoir electrode is positioned outside the device.

FIG. 9 shows an embodiment of another design of ionto-
15 therapeutic device. It shows two views of the device. The
first view is a cross-sectional view showing the integrated
circuitry, L.C. display, battery, drug reservoir electrode
20 positioned directly in the lower central portion of the base
and the receptor electrode encircling the drug reservoir
electrode. The next view shows the bottom view of the
25 device. In the center portion of the bottom view is shown
the circular drug reservoir portion of the drug reservoir
electrode. The drug or pharmaceutical dissolved in an
30 aqueous solution is homogeneously dispersed in a polymer
matrix unit dose as described herein. The pharmaceutical
35 solution can also be contained in a reservoir-type unit dose
having a microporous surface adapted to permit the drug to
be transmitted. Next, there is shown the receptor elec-
40 trode, as a circular ring positioned in spaced relationship
from the drug reservoir electrode. At the top of the cross-
45 sectional view is shown a liquid crystal display. It can
display a number of functions, including whether or not the
50 device is in operation, the type of periodic current and
waveform being used and other pertinent information of the
transdermal periodic iontotherapeutic drug delivery. The
55 battery employed as the power source for this invention can

5 be a lithium or other nuclear battery having a voltage, for example, of from 6 to 12 volts.

10 FIG. 10 is a block diagram of a portable transdermal periodic iontotherapeutic device in which the power supply is derived from a battery source such as one or more 9V
15 batteries. The power is turned on manually by a switch. The device can be equipped so that it can be turned on automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction
20 generators, a drug reservoir electrode and a receptor electrode. The multifunction generator can provide periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeutically effective waveform can be selected manually and
25 the frequency of the output waveform can be adjusted to a physiologically acceptable frequency of at least 10 Hz and up to about 50 KHz. The output circuit then provides a
30 physiologically acceptable current, ranging up to 10 mA, to the pharmaceutical reservoir electrode, which contains the solution of the ionized pharmaceutical to be delivered transdermally, and a receptor electrode in series. When
35 desired, the device can be operated to deliver either DC current alone (periodically or continuously), or in combination with a periodic waveform.

40
45
50
55 FIGS. 11 and 11A show a detailed circuit diagram for the portable transdermal periodic iontotherapeutic device shown in the block diagram of FIG. 10. Referring to FIG.

5

11, the following is a description of the circuits and their functioning:

10

The DC-to-DC converter and battery voltage monitor

15

1C₁, R₁-R₄, C₁-C₃, L1 and diode IN914 consist of a DC-to-DC converter which is incorporated in step-up application. The output voltage is elevated from 9V battery to 27V with the proper adjustment of R₄. The output voltage of the battery is monitored by a battery voltage monitor which includes a zener diode D₁, R₅-R₇, C₄ and C106Y1. When output of 9-V battery drops below minimum acceptable volume of 8.3V, LED lights to indicate the need for recharging.

25

30

Pulse generator and constant current output stage

35

IC₂, D₂-D₅, T₁, C₅, C₆ and R₈ are components of a triangle-wave generator. In this circuit, the charge and discharge currents for C₆ come through the diode bridge formed by D₂-D₅. Bridge D₂-D₅ consists of four general purpose switching diodes with low-leakage characteristics, that serve to steer current in the proper direction through the current source made up of T₁ and R₈.

40

45

50

55

The pin 3 of IC₂ serves as a source of current for the timing network, and its state of high or low determines the direction of current flow into or out of C₆ for charge or discharge. Since both charge and discharge currents flow through the same current regulator circuit, the currents are

5 equal, and thus times of charge and discharge are equal. As
a result, triangular waves are formed across C_6 .

10 The circuit covers the frequency range of about 20 Hz
to 30 KHz. The adjustment of the frequency is done with R_8 .
15 The frequency of the triangle waves can be expressed as

$$f = \frac{1}{5R_8C_6}$$

20 The output of the triangle-wave generator is sent to
the pin 3 of IC_3 which serves as a comparator. The voltage
comparison is made between pin 1 and pin 3 of IC_3 . The
25 square waves are formed at pin 7 of IC_3 with a duty cycle
which is determined by the voltage of the voltage divider
composed of R_{10} - R_{12} . The higher the voltage applied to pin
30 2 is, the shorter the "on" time of the square waves, and
vice versa. The duty cycle of the square waves covers the
35 range of 1/10 to 10/1. The square waves are amplified by
 T_2 - T_4 and sent to pin 11 of IC_4 .

40 In constant current output stage, IC_{923} is employed to
serve as a current regulator. IC_{923} is originally designed
to be a voltage regulator with an output current limit
45 resistor R across pin 10 and pin 3. The maximum output
current is set as $0.6/R$. This feature is adapted to form a
50 current regulator. As soon as the condition $(V_{out}/R_L) > I_S$ is
satisfied (where V_{out} is the output voltage, R_L , load resis-
tance, and I_S , output current preset), the output current
55 will be kept at the preset level.

5
10 R_{21} is the minimum current limit resistor. R_{22} is used to preset the desired output current. C_7 and R_{20} are used to eliminate high frequency noise.

Output current monitor

15 Intersil 7106 interfaced with a liquid crystal display is the heart of the current monitor. R_{23} is a shunt resistor. C_8 and R_{24} consist of an RC oscillator which runs at about 48 KHz and is divided by four prior to being used as the system clock. C_{10} and R_{27} serve as an input filter. 25 C_{11} , C_{12} and R_{28} determine the display sensitivity. C_9 is for auto-zero function.

30 The power is turned on manually by a switch or automatically by a programmable timer. The device also consists of one or a combination of several electronic multifunction generators, a drug reservoir electrode and a receptor electrode. 35 The multifunction generator is assembled with a power supply, to deliver direct current with periodic waveform of either square, triangular, trapezoidal or sinusoidal shape, to an output circuit. The desired iontotherapeuti- 45 cally effective waveform can be selected manually or programmed through a switch (K_1), and the frequency of the output waveform can be adjusted in the range of 10 Hz - 50 50 KHz. The output circuit then provides a physiologically acceptable current, ranging up to 10 mA, to the pharmaceutical reservoir electrode, which contains the pharmaceutical 55 formulation to be delivered transdermally, and a receptor

5 electrode in series. When desired, the device can be
operated to deliver either DC current alone (periodically or
10 continuously), or in combination with a periodic waveform.

FIG. 12 is a detailed circuit diagram for the timer of
15 the multi-channel transdermal periodic iontotherapeutic
device shown in the block diagram of FIG. 12. Referring to
FIG. 12, the following is a description of the circuit, and
20 their functioning:

Timer

25 The timer consists of ten IC chips, two relays and
other components, IC₈ provides a system clock. IC₁, IC₃ and
30 IC₅ are quad 2-input multiplexers which consist of four 2-
input multiplexers with common select and enable inputs.
When the select input is at logical "0", the four output
35 pins assume the values of inputs of pin 1, 5, 14, 11, other-
wise, inputs of pin 3, 6, 13, 10. The inputs of the first
group represent the "off" time of the timer which has a
40 maximum value of 999 minutes. The inputs of the second group
represent the "on" time of the timer which has a maximum
45 value of 99 minutes. The values of both "on" and "off" time
needed are set through BCD thumbwheels.

50 IC₂, IC₄ and IC₆ are "decade-down" counters which
receive preset values from multiplexers. The pin 15's of
these counters will become logical "0" when the minimum
55 count is reached. When all three counters reach the mini-
mum, IC₉, a "AND" gate, will turn to be logical "1". This

5 pulse is inverted by IC_{10} and goes to reset the system
clock, reloads counters and converts IC_7 , which consists of
10 two Flip-Flop's. At the instant when "on" time is finished,
the pin 3 and pin 5 turn to be logical "0", which opens two
15 relays and turns on the red LED. At the same time, the pin
2 and pin 6 turns to be logical "1", which will load the
values representing the "on" time to pin 4, 7, 9, 12 of
20 three multiplexers and turns off the green LED. At the
instant when "off" time is finished, the pin 3 and pin 5
25 turn to be logical "1", which will load the values repre-
senting the "off" time to pin 4, 7, 9, 12 of three multi-
plexers and turns on the green LED. The whole cycle of both
30 "on" and "off" is repeated for any desired length of time.
The switch K_2 is used to interrupt the operation and trigger
35 the timer.

Pulse generator and constant current output stages

40 IC_{13} , diode bridge consisting of four IN_{914} , T_1 , R_{28}
and C_5 - C_7 are components of a triangle wave generator. In
this circuit, the charge and discharge currents for one of
45 C_6 - C_{17} come through the diode bridge formed by four IN_{914} ,
which serve to steer current in the proper direction through
the current source made up of T_1 and R_{28} .
50

The pin 3 of IC_2 serves as a source of current for the
timing network, and its state of high or low determines the
55 direction of current flow into or out of the capacitor for
charge or discharge. Since both charge and discharge cur-

5 rents flow through the same current regulator circuit, the
currents are equal and thus times of charge and discharge
10 are equal. As a result, triangular waves are formed across
the working capacitor C.

15 The circuit covers the frequency range of about 10 Hz
to 30 KHz. The adjustment of the frequency is done by the
selection of the proper capacitor through a multi-stop
20 switch. The frequency of the triangle waves can be
expressed as

$$25 \quad f = \frac{1}{5R_{28}C}$$

The output of the triangle wave generator is sent to
30 the pin 3 of IC₁₄ which serves as a comparator. The voltage
comparison is made between pin 2 and pin 3 of IC₁₄. The
square waves are formed at pin 7 of IC₁₄ with a duty cycle
35 which is determined by a voltage-divider composed of R₃₂₂-
R₃₄. The higher the voltage applied to pin 2 is, the short-
40 er the "on" time of the square waves, and vice versa. The
duty cycle of the square waves covers the range of 1/10 to
10/1. The square waves are amplified by T₂ and T₃ and then
45 sent to three voltage followers T₄-T₆.

At the "on" time of the timer, two relays are closed
50 and emitters of T₄-T₆ are connected to pin 11's of IC₁₅-
IC₁₇. IC₁₅-IC₁₇ provide three-channel current outputs.
Three IC₉₂₃ are employed to serve as current regulators.
55 IC₉₂₃ is originally designed to be a voltage regulator with
an output current limit resistor R across pin 10 and pin 3.

5 The maximum current is set as $0.6/R$. This feature is
adapted to form a current regulator. As soon as the condi-
10 tion $(V_{out}/R_L) > I_S$ is satisfied (where V_{out} is the output
voltage, R_L load resistance and I_S output voltage, R_L load
15 resistance and I_S output current preset), the output current
will be kept at the present level. R_{40} , R_{45} and R_{50} are
maximum current limit resistance respectively. R_{41} , R_{46} and
20 R_{51} are used to preset the desired current. C_{19} - C_{21} are
used to eliminate high frequency noise.

25 The output currents are monitored by a current meter A.
The switch K_1 is used to select DC or pulse output. Other
circuits can be used in place thereof.

30 FIG. 13 is a schematic diagram of a device of this
invention. It shows a wristwatch-type device which houses
35 the iontotherapeutic device in the center in connection with
a belt-type battery package. The display unit, emergency
on/off switch, the input/output port, the interface cable to
40 a computer system, and the sensor input port are also shown.
This device can be comfortably worn by a patient during the
45 treatment. The weight of such device of this invention will
ordinarily be 5 oz. or less, preferably 3 oz. or less.

50 FIG. 14 is a schematic diagram of a wrist-type ionto-
therapeutic device of this invention showing a connection
with a computer patient data and control system such as at a
55 clinical site or at a physician's office. The communication
between the iontotherapeutic device and a computer system

5 serves two purposes. It allows the commands and data
according to the physician's prescription to transfer to the
10 iontotherapeutic device via an interface cable. It also
allows the physician to read and assess the important data
of treatment using the device. By using telephone lines,
15 the communication can be to a remote site.

Various computers are satisfactory for use in the com-
puter system, including personal computers and larger compu-
20 ters. Various suitable programs can be used in the communi-
cation.

25 FIG. 15 is the schematic diagram of an iontotherapeutic
device of this invention using a belt or band to attach to
the subject being treated. Inside the belt there are bat-
tery elements connected in series. These batteries can be
either regular ones or rechargeable ones. The battery belt
35 can also be made into a shape of jewelry. The battery belt
can be designed to house different numbers of battery ele-
ments to power different treatment periods. The belt can be
40 made of suitable material such as plastic or leather mate-
rials or metals or combinations of materials. Its length
45 can be adjusted as needed.

FIG. 16 is a graph showing the time course for the
50 reduction of the elevated blood glucose level (% change in
B.G.L.) in the diabetic hairless rats as the result of
transdermal delivery of insulin from the drug reservoir
55 electrode (containing 250 IU of insulin at pH 7.1) by Trans-
dermal Periodic Iontotheapeutic System for 80 minutes and

5

10

the effect of current delivery mode. Keys: (O) direct current mode (2 mA), () Square wave periodic mode (2 mA; on/off = 4/1; Frequency = 2000 Hz).

15

20

25

FIG. 17 is a graph showing the time course for the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats as the result of transdermal delivery of insulin from the pharmaceutical reservoir electrode (containing 250 IU of insulin at pH 3.6) by Transdermal Periodic Iontotherapeutic System with square wave periodic mode (1 mA; on/off = 1/1; Frequency = 2000 Hz) for 40 minutes.

30

35

40

FIG. 18 is a graph showing the effect of the frequency generated by the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats. The frequency of 2000 Hz produces a greater magnitude and a longer duration of reduction than the 1000 Hz.

45

50

FIG. 19 is a graph showing the effect of the on/off ratio in the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (% change in B.G.L.) in the diabetic hairless rats. By regulating the ratio, the magnitude and the duration of reduction in B.G.L. in the diabetes can be controlled as desired.

55

FIG. 20 is a graph showing the effect of the treatment duration by the Transdermal Periodic Iontotherapeutic System on the reduction of the elevated blood glucose level (%

5 change in B.G.L.) in the diabetic hairless rats. At pH 3.6,
which is lower than the isoelectric point of insulin (pH
10 5.3), with the dose current of 1 mA, on/off ratio of 8/1 and
at a frequency of 2000 Hz, the treatment duration of 20-40
minutes appears to be equally effective.

15 FIG. 21 is a graph showing the effect of the treatment
duration by the Transdermal Periodic Iontotherapeutic System
20 on the reduction of the elevated blood glucose level (%
change in B.G.L.) in the diabetic hairless rats. AT pH 7.1,
25 which is higher than the isoelectric point of insulin (pH
5.3), with the dose current of 1 mA, on/off ratio of 1/1 and
at frequency of 1000 Hz, the treatment duration produces a
30 difference in the rate and the duration, but with equal
effectiveness.

35 For a more detailed description of the background for
the remaining FIGS., see the indicated Examples: FIG. 22
(Example 11); FIGS. 23A and 23B (Example 12); FIG. 24
40 (Example 14); FIG. 25 (Example 15); FIGS. 26A and 26B
(Example 16); FIG. 27 (Example 17); FIG. 28 (Example 18);
FIG. 29 (Example 19); FIG. 30 (Example 20).

45 In carrying out the iontotherapeutic process for admin-
istering transdermally, systemically measured amounts of an
50 ionized pharmaceutical compound, it is first necessary to
provide the pharmaceutical-containing unit dose in which the
pharmaceutical is in aqueous solution. The pH of the
55 aqueous solution is adjusted to an effective Ph either below
or above the pKa or the isoelectric point of the pharmaceu-

5

10

15

20

25

30

35

40

45

50

55

tical. It is desirable to adjust the pH to an effective level of about 1 pH unit above or below the pKa or isoelectric point of the pharmaceutical, preferably to an effective pH level of at least 1.5 or at least 2 pH units below or above the pKa or isoelectric point of the pharmaceutical. With particular pharmaceuticals, it is preferable to so adjust the pH either below or above the pKa or isoelectric point. For example, with regard to insulins, it is preferable to adjust the pH below the pKa or isoelectric point, such as to about 1.0 pH units or lower below, which for commercial insulins is about pH 5.3.

The formed unit dose is placed in the receptacle portion provided in the pharmaceutical reservoir electrode, so that the ionized pharmaceutical can be transdermally absorbed. If the unit dose form is a preformed self-contained unit dose, it can be held in the receptacle portion of the reservoir electrode by customary means such as clamping, snapping into position, adhesive, or the like.

One convenient form of the unit dose for the ionized pharmaceutical solution is to disperse uniformly the aqueous solution of the ionized pharmaceutical in a polymeric matrix. The polymeric unit dose must be characterized by being able to release the ionized pharmaceutical, when the iontotherapeutic device is in operation, so that the ionized pharmaceutical can be absorbed transdermally. The unit dose

5

is in electrical contact with the skin of the subject being treated when the iontotherapeutic device is in operation.

10

For a description on making suitable unit dose in the form of a polymeric matrix dosage unit, reference is made to parent U.S. Application Serial No. 07/046,984, filed May 5, 1987, now U.S. Patent Application No. 5,042,975, which is incorporated herein by reference.

15

20

Additionally, descriptions are found in parent U.S. Application Ser. No. 07/587,406, filed September 25, 1990, which is incorporated herein by reference.

25

30

The pharmaceuticals suitable for delivery by this polymer disc can be the anti-diabetic drugs, such as insulins or sulfonyl ureas; the anti-diuretic peptide drugs, such as vasopressin; the calcium-channel blocker-type anti-hypertensive drugs, such as verapamil; the beta-blocker type anti-hypertensive drugs, such as propranolol; narcotic analgesic drugs, such as hydrocodone; non-steroidal anti-arthritic drugs, such as indomethacin; anti-bacterial antibiotics, such as tetracyclines, penicillins and cephalosporins; anti-neoplastic drugs, such as methotrexate; and the peptide hormones, such as luteinizing hormone-releasing hormone (LHRH), oxytocin, and the like.

35

40

45

50

55

Pharmaceuticals suitable for use in the process of this invention can be selected from the following or other ionizable pharmaceuticals which are capable of being transdermally absorbed in the iontotherapeutic process, the following systemically-effective pharmaceuticals expected to be

5

10

15

20

25

30

35

capable of delivery by an iontotherapeutic device as developed in this invention: Propranolol HCl, Ibuprofen, Indomethacin HCl, Lorazepam, Thioridazine HCl, Tolazamide, Doxycycline, Flurazepam, Minocycline, Disopyramide, Metoclopramide HCl, Cephalothin sodium, Thiethixene, Vincristine, Oxazepam, Valproic acid, Temazepam, Hydralazine HCl, Ampicillin sodium, Amantadine HCl, Acetohexamide, Haloperidol, Doxepin, Cyclobenzaprine HCl, Sucralfate, Cephalaxin, Cefazolin sodium, Ampicillin, Cefadroxil, Hydralazine HCl, Reserpine and Hydrochlorthiazide, Clindamycin HCl, Carbenicillin disodium, Piroxicam, Fenoprofen calcium, Diltiazem HCl, Chlorpropamide, Sulindac, Nifedipine, Cimetidine, Naproxen, Piroxicam, Ranitidine HCl, Nadolol, Alprozalam, Captopril, Triazolam, Chlordiazepoxide, Amitriptyline, Dobutamide, Sulfamethoxazole, Trimethoprim, and the like.

40

45

The ionizable peptide pharmaceuticals used in the processes and the unit doses of this invention and administered by the devices of this invention are those which are pharmaceutically effective and transdermally absorbable. Desirably the peptides have at least five amino acid units and more desirably at least nine amino acid units.

50

55

In operating the process, using for example a wrist-watch-type iontotherapeutic device such as provided by this invention, the appropriate unit dose containing the pharmaceutical required for the desired therapy is assembled in the receptacle portion of the pharmaceutical reservoir elec-

5 trode. For example, if insulin is to be administered and
the pH of the insulin solution in the dose unit is pH 3.6,
10 insulin is a cationic and therefore the dosage unit is
assembled as a part of pharmaceutical reservoir electrode,
15 which is the anode. The desired waveform is selected and
preprogrammed, such as a square waveform. The pharmaceuti-
cal reservoir electrode used preferably is adapted to
20 receive a disposable unit dose, e.g., a polymeric matrix
unit dose, and to make electric contact with the skin of the
25 subject being treated. Such means is assembled in place.
The other variables are selected and preprogrammed, such as
the frequency, the dose current and on/off ratio. The
30 device is attached to the subject being treated as by a band
attached to the device and adapted to be attached to and
35 detached from the subject. The switch of the device is
turned to "on" position and the device commences operation
of the iontotherapeutic process, which causes the ionized
40 pharmaceutical of reservoir electrode to be administered
transdermally and iontotherapeutically to provide a systemic
45 dosing. The particular waveform, mA, pharmaceutical reser-
voir electrode (i.e., cathode or anode), frequency, length
of treatment and other factors will be selected and prepro-
50 grammed depending upon the pharmaceutical being admin-
istered, the subject being treated and others.

55 Some pharmaceuticals, especially certain relatively low
molecular weight pharmaceuticals, can be iontotherapeuti-
cally administered using either periodic DC mode or periodic

5

10

15

20

25

30

35

40

45

50

55

wave mode. For example, the periodic DC mode can be "on" for about 0.5 to about 10 minutes, preferably about 1 to about 5 minutes per hour. During the intervening period during the hour, the device is in "off" position. The "on" period can be more frequent or less frequent, if desired, to provide effective treatment, such as one "on" period every 30 minutes or every ninth minute. In Example 5, it is shown that hydrocodone can be administered following this general procedure. The dose currents, the on/off ratios, the dosage units and the devices described above can be used or adapted to be used in the practice of the periodic DC mode process.

A few hours duration of treatment each day following either procedure is ordinarily adequate, for example, 2 to 10 hours, depending upon factors such as the pharmaceutical, the subject being treated, the iontotherapeutic factors selected and the like.

5

The following Examples are illustrative of the invention but are not intended to be limiting.

10

Example 1

An aqueous solution of insulin at concentration of 250 IU/ml is prepared by dissolving 96.9 mg (25.8 IU/mg) of pure insulin in 10 ml of double-distilled, sterile water and adjusted to pH 7.1 with 0.5N NaOH. Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This insulin-containing reservoir-type dosage unit is then assembled as a part of the pharmaceutical reservoir electrode and applied on the abdominal skin of 3 diabetic hairless rats with the transdermal periodic iontotherapeutic system operating at 2 mA with direct current mode or square-wave periodic mode (on/off = 4/1; Frequency = 2000 Hz). The results on the reduction in blood glucose level are shown and compared in FIG. 16.

40

Example 2

An amount of 200 mg (25.8 IU/mg) of pure insulin is dissolved in 10 ml of double-distilled, sterile water and the pH is adjusted to 3.6 with 0.5N HCl. An amount of 200 mg of hydroxypropylmethylcellulose is well dispersed in another 10 ml of double-distilled sterile water using a magnetic stirrer with a stirring bar (5 cm in length) at a rotation speed of 600 rpm. The temperature is controlled at

55

5 about 80°C. After the hydroxypropylmethylcellulose is dis-
persed homogeneously, the stirring is continued while the
10 mixture is cooled to about 40°C.

 The insulin solution prepared above is then added to
15 the dispersion of hydroxypropylmethylcellulose with inter-
mittent stirring to avoid any denature of insulin molecules,
using the same stirring mechanism as described above, at the
20 same stirring rate of 600 rpm for a period of two minutes.
The insulin/hydroxypropylmethylcellulose solution is then
25 placed in a refrigerator for congealing to occur. The insu-
lin-containing polymer matrix is cut into disc-shaped parts
with the appropriate dimensions, such as 2.5 cm in diameter
30 and 0.2 cm in thickness. The insulin-containing discs are
stored at 5°C. The concentration of insulin in the discs is
about 250 IU/gm.

35 The insulin-containing polymeric matrix dosage forms
are removed as needed and assembled into the pharmaceutical
40 reservoir electrode. The pharmaceutical reservoir electrode
having the insulin-containing polymer unit dose form is the
45 anode since the insulin molecules in the polymeric matrix
dose units are cations at pH 3.6, which is lower than the
isoelectric point of insulin (pH_{iso} = 5.3).

50 Application of this insulin-containing polymeric matrix
unit dose is made onto the abdominal skin of 3 diabetic
hairless rats. The transdermal periodic iontotherapeutic
55 system is then operated at 1 mA using an on/off ratio of
1/1, a frequency of 2000 Hz and a square wave mode, for 40

5

minutes. The result on the reduction in blood glucose level is shown in FIG. 17.

10

Example 3

15

An aqueous solution of insulin at a concentration of 250 IU/ml is prepared by dissolving 193.8 mg (25.8 IU/mg) of pure porcine insulin in 20 ml of citrate buffer at pH 3.6.

20

Two ml of the insulin solution so prepared is filled into a refillable dosage unit having a microporous membrane as the drug-releasing surface. This insulin-containing reservoir-

25

type dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device

30

and applied successively on the abdominal skin of 9 diabetic hairless rats with the transdermal periodic iontotherapeutic system operating at 1 mA with square waveform mode to study

35

the effect of frequency, on/off ratio and treatment duration on the reduction of blood glucose level. The results are

40

shown and compared, respectively in FIGS. 18, 19 and 20.

Example 4

45

The same insulin solution is prepared in the same way as in Example 1, except that a phosphate buffer at pH 7.1 is

50

used to replace the double-distilled water. Two ml of the insulin solution so prepared is filled into a refillable

55

dosage unit having a microporous membrane as the drug-releasing surface. This unit dose is applied to 3 diabetic hairless rats following the same operation procedures as in

5
10 Example 3 to study the effect of treatment duration on the reduction of blood glucose level. The results are shown in FIG. 21.

15 Example 5

20 A saturated solution of hydrocodone ($pK_a = 8.56$), a narcotic analgesic drug, is prepared in citrate buffer at pH 4.0 and in phosphate buffer at pH 7.5. An aliquot of 3.5 ml of this hydrocodone solution is filled into the reservoir compartment, which is in contact with the stratum corneum surface of the hairless rat abdominal skin, of each Valia-Chien skin permeation cell with the receptor compartment containing equal volume of a pH 7.4 buffered isotonic (drug-free) saline solution. The transdermal periodic iontopherapeutic system is then mounted with its electrodes immersing in the skin permeation cell, one electrode in each of the two solution compartments. A current of 1 mA is applied for 2 min. periodically on the hour for 12 hours at either DC mode or periodic square wave mode (frequency, 2000 Hz; on/off ratio, 1/1). The results are shown in Table I.

45
50
55

Table I: Enhancement in Rate and Reduction in Time Lag of the Skin Permeation Rate of Hydrocodone, a Narcotic Analgesic Drug, by the Transdermal Periodic Iontotherapeutic System

<u>Skin Permeation Rate</u> (mcg/cm ² /hr \pm S.D.)			
Mode	pH 7.5	pH 4.0	T _{lag} (hrs)
Control	4.75 \pm 1.70	3.10	5.17
DC mode	7.61 \pm 2.74	37.5	0.72
periodic wave mode	7.01 \pm 1.16	59.4	0.90

Example 6

A saturated solution of methotrexate, an anti-neoplastic drug, is prepared in double-distilled water and adjusted to pH 8.0, which is higher than the pKa values of methotrexate (4.8 and 5.5). An aliquot of 3.5 ml of this methotrexate solution (2 mg/ml) is filled into the donor compartment, which is in contact with the stratum corneum surface of the hairless rat abdominal skin, of each Valia-Chien skin permeation cell with the receptor compartment containing equal volume of a pH 7.4 buffered isotonic (drug-free) saline solution. The transdermal periodic iontotherapeutic system is then mounted with its electrodes immersed in the skin permeation cell, one electrode in each of the two solution compartments. A DC current of 1 mA is applied for 10 minutes periodically on the hour for 5 hours with a frequency of 2000 Hz, a square wave form, and an on/off ratio of 4/1. The results are illustrated in Table II:

Table II: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Methotrexate - An Anti-Neoplastic Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm ²)	
	<u>No TPIS</u>	<u>With TPIS</u>
1.33	0.0086	0.0820
2.33	0.0247	0.1373
3.33	0.0471	0.4223
4.16	0.0745	0.5705
5.16	0.1398	1.0835

Example 7

A saturated solution of propranolol (pKa = 9.45), a beta-blocker type anti-hypertensive drug, is prepared in citrate buffer at pH 3.68. The enhancing effect of the transdermal periodic iontotherapeutic system is studied under the same conditions as that outlined in Example 6. The results are shown in Table III:

Table III: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Propranolol (1) - An Anti-Hypertensive Beta-Blocker Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm ²)	
	No TPIS	With TPIS ⁽²⁾
1.5	0.0691	0.5970
2.5	0.2615	1.1950
3.5	0.5845	3.3650
4.5	0.9955	5.2150
5.5	2.0800	9.0700

- 1) In the Valia-Chien skin permeation cell, a donor solution containing 13.3 mg/ml of propranolol (pKa = 9.45) at pH 3.68 was applied topically to hairless rat skin at 37°C.
- 2) TPIS applied a DC current of 1mA periodically at 10 min/hr, a frequency of 2000 Hz and an on/off ratio of 4/1.

Example 8

A saturated solution of verapamil (pKa = 8.9), a calcium-channel blocker-type anti-hypertensive drug, is prepared in citrate buffer at pH 3.68. The enhancing effect of the transdermal periodic iontotherapeutic system is studied under the same conditions as that outlined in Example 6. The results are shown in Table IV.

Table IV: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Verapamil⁽¹⁾ - A Calcium-Channel Blocker-Type Antihypertensive Drug

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm ₂)	
	No TPIS	With TPIS ⁽²⁾
1.42	<0.0001	0.297
2.42	<0.0001	0.445
3.42	-	0.695
4.17	-	0.973
5.17	<0.0001	1.945

- 1) In the Valia-Chien skin permeation cell, a donor solution containing 23.95 mg/ml of verapamil (pKa = 8.9) at pH 3.68 is applied topically to hairless rat skin at 37°C.
- 2) TPIS applied a DC current of 1 mA periodically at 10 min/hr, a frequency of 2000 Hz and an on/off ratio of 4/1.

Example 9

A saturated solution of tetracycline HCl (pKa = 3.3, 7.8 and 9.7), an antibiotic drug, is prepared in phosphate buffer at pH 9.0. The enhancing effect of the transdermal periodic iontotherapeutic system is investigated under the same conditions as that outlined in Example 6. The results are shown in Table V:

Table V: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Tetracycline HCl₍₁₎ - A Calcium-Channel Blocker-Type

Time (hrs)	Cumulative Amount of Drug Absorbed (mcg/cm ₂)	
	<u>No TPIS</u>	<u>With TPIS</u> (2)
1.25	0.0180	0.1765
2.25	0.0550	0.2555
3.25	0.0650	0.7815
4.25	0.1450	1.3235
5.25	0.3040	3.5600

1) In the Valia-Chien skin permeation cell, a donor solution containing 6.2 mg/ml of tetracycline HCl (pKa = 3.3, 7.8 and 9.7) at pH 9.0 is applied topically to hairless rat skin at 37°C.

2) TPIS applied a DC current of 1 mA periodically at 10 min/hr, a frequency of 2000 Hz, a square waveform and an on/off ratio of 4/1.

Example 10

A saturated solution of indomethacin (pKa = 4.5), a non-steroidal anti-arthritic drug, is prepared in buffer solution at pH 2.5, which is 2 pH units below the pKa, and at pH 5.5, which is one pH unit above the pKa, and at pH 4.5, the pKa. The enhancing effect of the transdermal periodic iontotherapeutic system is evaluated under the same conditions as that outlined in Example 6. The results are shown in Table VI.

Table VI: Enhancing Effect of Transdermal Periodic Iontotherapeutic System (TPIS) on the Skin Permeation of Indomethacin - A Non-Steroidal Anti-Arthritic Drug

TPIS*	Skin Permeation Rate (mcg/cm ₂ /hr)		
	<u>pH 2.5</u>	<u>pH 4.5</u>	<u>pH 5.5</u>
No	-	-	1.47
Yes	0.76	0.44	6.30

*TPIS applied a DC current of 1.2 mA periodically at 5 min/hr, for 7 hours, with a frequency of 2000 Hz, a square waveform and an on/off ratio of 2/1.

Example 11

An aqueous buffer solution of vasopressin (50 mcg/ml containing 1.7 mCi/ml H₃-vasopressin) is prepared in citrate-phosphate buffer at pH 5.0. An aliquot of 3.5 ml of this vasopressin solution is filled into the refillable dosage unit having a microporous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permeation cell at 37°C. Samples are withdrawn at regular intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed.

5 The results demonstrate that vasopressin permeates
through the hairless rat skin at constant, but slow rate for
10 30 hours (0.94 ± 0.62 ng/cm₂/hr) (FIG. 22).

15 When the skin is treated with transdermal periodic
iontophoretic system (TPIS) at current intensity of 0.5 and
1mA, frequency of 2 KHz, on/off ratio of 1/1, and at the
rate of 10 min. per 40 min. for 4 hours, the skin permeation
20 profiles are enhanced with rate increases from 0.94 (± 0.62)
ng/cm₂/hr (referred to as "passive diffusion" in FIG. 20) to
116.2 (± 10.7) and 178.0 (± 25) ng/cm₂/hr, respectively.
25 After the treatment with transdermal periodic iontophoretic
system, referred to in following Table VII as "post-activation
30 phase," the rate of skin permeation of vasopressin is
reduced to the basal rate of only 0.7 (± 0.4) and 5.3 (\pm
0.5) ng/cm₂/hr, respectively. The results of the experiment
35 are shown in FIG. 22 and in the following Table VII.

40

45

50

55

Table VII: Effect of TPIS on Skin
Permeation Rate of Vasopressin

No TPIS	0.0 mA	9.12 (± 1.06)	0.94 (± 0.62)
With TPIS			
a) Activation phase ₍₂₎	0.5 mA	<0.5	116.2 (± 0.4)
b) Post-Activation phase	0.0 mA	---	0.7 (± 0.4)
a) Activation phase ₍₂₎	1.0 mA	<0.5	178.0 (± 25.0)
b) Post-Activation phase	0.0 mA	---	5.3 (± 0.5)

1) In-vitro permeation across hairless rat skin mounted in the Valia-Chien permeation cell.

2) Application of DC at on/off ratio of 1/1 and frequency of 2 KHz, by multi-channel TPIS unit (shown in FIG. 22 for 10 min. per 40 minute period, treatment repeated for six 40-minute cycles.

Example 12

An aqueous solution of insulin (5.3 IU/ml containing 0.3 mCi of I₁₂₅-insulin) is prepared and adjusted to pH 7.1 using NaOH. An aliquot of 3.5 ml of this insulin solution is filled into the refillable dosage unit having a micro-porous membrane as the drug-releasing surface. The dosage unit is then assembled as a part of the pharmaceutical reservoir electrode of the iontotherapeutic device and membrane surface thereof is applied to the stratum corneum side of hairless rat skin mounted in the Valia-Chien skin permea-

5 tion cell at 37°C. Samples are withdrawn at regular time
intervals and radioactivity is measured by scintillation
10 counter to determine the amount of insulin which has been
transdermally absorbed.

15 The results demonstrate that insulin permeates through
the hairless rat skin at constant, but at a slow rate for 48
hours (3.94 ± 0.29 mcIU/cm₂/hr) (FIG. 23A).

20 When the skin is treated with transdermal therapeutic
system (TIDD) at current intensity of 1mA, frequency of 0
25 Hz, on/off ratio of 1/1, and at the rate of 5 min. per 60
min. for 7 hours, the skin permeation profiles are enhanced
with rate increased from 3.94 (± 0.29) mcIU/cm₂/hr to 37.5
30 (± 4.5) mcIU/cm₂/hr. FIG. 23B shows comparison of insulin
permeation data in FIG. 23A using no iontotherapy (0) over a
35 7-hr. period with permeation data of same insulin solution
using TIDD iontotherapy.

40 Example 13

45 An aqueous solution of insulin (5.3 IU/ml containing
0.3 mCi of I₁₂₅-insulin) is prepared and adjusted to pH
3.7, 5.2 or 7.1 using either HCl or NaOH solution. An
aliquot of 3.5 ml of this insulin solution is filled into
50 the refillable dosage unit having a microporous membrane as
the drug-releasing surface. The dosage unit is then
55 assembled as a part of the pharmaceutical reservoir elec-
trode of the iontotherapeutic device and membrane surface

5 thereof is applied to the stratum corneum side of hairless
rat skin mounted in the Valia-Chien skin permeation cell at
10 37°C. Samples are withdrawn at regular time intervals and
radioactivity is measured by scintillation counter to deter-
mine the amount of insulin which has been transdermally
15 absorbed.

 The results demonstrate that insulin permeates through
20 the hairless rat skin at constant, but at a slow rate for 48
hours, with permeability coefficient ranging from 6.50
(± 4.2) to 10.02 (± 1.94) $\times 10^{-7}$ cm/hr (Table VIII).
25 Permeability coefficient is the ratio of the steady state
rate of skin permeation of the pharmaceutical which is
transdermally absorbed/the concentration of the pharmaceuti-
30 cal solution which is applied transdermally. The pharmaceu-
tical in this experiment is insulin.

35 When the skin is treated with transdermal therapeutic
system (TIDD) at current intensity of 1mA, frequency of 0
40 Hz, on/off ratio of 1/1, and at the rate of 5 min. per 60
min. for 7 hours, the skin permeation profiles are enhanced
with skin permeability coefficient increased to a range from
45 70.76 (± 8.56) $\times 10^{-7}$ to 242.59 (± 18.43) $\times 10^{-7}$ cm/hr, which
show dependence on solution pH. The lower pH solution (pH
50 3.7) shows greater increase in TPIS-facilitated skin per-
meability.

Table VIII: Skin Permeability Coefficient of Insulin
(Hairless Rats)

	Donor Solution	Permeability Coefficient (1) (cm/hr \pm SE) $\times 10$	
	<u>pH</u>	<u>No TIDD</u>	<u>With TIDD</u>
15	3.7	6.50 (± 1.42)	242.59 (± 18.43)
	5.2	10.02 (± 1.94)	120.07 (± 22.86)
	7.1	7.43 (± 0.54)	70.76 (± 8.56)

5 the blood glucose levels are reduced substantially. The
data show that the time course and the extent of reduction
10 in blood glucose levels in diabetic rats vary with the type
of waveform used (FIG. 24).

15
Example 15

20 An aqueous buffer solution of insulin (250 IU/ml) is
prepared in citrate-phosphate buffer at pH 3.68. An aliquot
of 2.5 ml of this insulin solution is filled into the
25 refillable dosage unit having a microporous membrane as the
drug-releasing surface. The dosage unit is then assembled
as a part of the pharmaceutical reservoir electrode of the
30 iontotherapeutic device and membrane surface thereof is
applied to the skin at abdominal region of 5 anesthetized,
35 diabetic hairless rats. Blood samples are withdrawn at
regular time intervals and glucose levels are measured by
glucose analyzer. The reduction in glucose level from
40 hyperglycemic state is the pharmacodynamic response to the
insulin absorbed transdermally. The results demonstrate
45 that when the skin is treated on Day 1 with transdermal
periodic iontophoretic system (TPIS) with insulin in the
pharmaceutical reservoir electrode at current intensity of 1
50 mA, frequency of 2 KHz, square waveform, on/off ratio of
1/1, for 40 min. the blood glucose levels are reduced sub-
55 stantially (FIG. 25A). On Day 3, the diabetic rats are
treated again with TPIS with no insulin in the pharmaceuti-

5 cal reservoir electrode (placebo formulation), the blood
glucose is also reduced, indicating that part of the insulin
10 delivered transdermally on Day 1 forms a depot in the skin
tissue and can be triggered to be systemically absorbed on
Day 3 (FIG. 25B).

15 Example 16

20 An aqueous buffer solution of insulin (500 IU/ml) at pH
7.10 is used. An aliquot of 2.5 ml of this insulin solution
is filled into the refillable dosage unit having a micro-
25 porous membrane as the drug-releasing surface. The dosage
unit is then assembled as a part of the pharmaceutical
30 reservoir electrode of the iontotherapeutic device and mem-
brane surface thereof is applied to the skin at dorsal
region of 3 diabetic rabbits. Blood samples are withdrawn
35 at regular time intervals and analyzed for immunoreactive
insulin concentration by radioimmunoassay and for glucose
40 levels by glucose analyzer. The reduction in glucose level
from hyperglycemic state is the pharmacodynamic response to
the insulin absorbed transdermally. The results demonstrate
45 that when the skin is treated with transdermal periodic
iontophoretic system (TPIS) at current intensity of 1 mA,
50 frequency of 2 KHz, on/off ratio of 1/1, and square waveform
for 40 min. the plasma immunoreactive insulin concentration
increases rapidly and the blood glucose levels are reduced
55 substantially. The plasma insulin profile (FIG. 26A) as
well as the time course and the extent of reduction in blood

5 glucose levels (FIG. 26B) in diabetic rabbits are compared
with the results from the conventional subcutaneous adminis-
10 tration of insulin. The data show that plasma insulin con-
centrations as well as blood glucose levels can be effec-
15 tively controlled using TPIS system of this invention. FIG.
24B shows that by using the TPIS system of this invention
the blood glucose level (B.G.L.) can be appropriately
20 reduced in a more controlled manner than by daily SC dosages
so as to prevent B.G.L. to fall below normal levels.

25 Example 17

30 An aqueous buffer solution of insulin (500 IU/ml) at pH
7.10 is used. An aliquot of 2.5 ml of this insulin solution
is filled into the refillable dosage unit having a micro-
35 porous membrane as the drug-releasing surface. The dosage
unit is then assembled as a part of the pharmaceutical
reservoir electrode of the iontotherapeutic device and mem-
40 brane surface thereof is applied to the skin to the
abdominal skin of 2 groups of diabetic rabbits. Blood
45 samples are withdrawn at regular time intervals and analyzed
for immunoreactive insulin concentration by radioimmunoassay
and for glucose levels by glucose analyzer. The reduction
50 in glucose level from hyperglycemic state is the pharmaco-
dynamic response to the insulin absorbed transdermally.
55 The results demonstrate that when the skin is treated with
transdermal periodic iontophoretic system (TPIS) at current

5 intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1,
and square waveform for 40 min., the plasma immunoreactive
10 insulin concentration increases more rapidly and the blood
glucose levels are reduced more instantaneously than trans-
dermal iontophoretic delivery (TIDD) at current intensity of
15 4 mA for 80 min. (FIG. 27). The data in FIGS. 25A and B
show that the TPIS system of this invention provides both a
20 more rapid increase in plasma insulin concentration after
administration and a more rapid reduction in blood glucose
level than use of TIDD even though the corresponding current
25 intensity in the TIDD system is 4 times as much (4 mA vs. 1
mA) and administration is 2 times as great (80 minutes vs.
30 40 minutes) as in the TPIS system.

Example 18

35 An aqueous buffer solution of vasopressin (40 IU/ml) is
prepared in citrate-phosphate buffer at pH 5.0. Vasopressin
40 is an anti-diuretic pharmaceutical, which is used by
patients which have an excessive urine output. Vasopressin
caused a reduction of urine output and an increase in ion
45 content, such as sodium ion content. Ion content in the
urine is determined by using osmolarity measurement. An
50 aliquot of 3.5 ml of this vasopressin solution is filled
into the refillable dosage unit having a microporous mem-
brane as the drug-releasing surface. The dosage unit is
55 then assembled as a part of the pharmaceutical reservoir
electrode of the iontotherapeutic device and membrane sur-

5 face thereof is applied to the abdominal skin of 2 groups of
anesthetized rabbits. Blood samples are withdrawn and urine
10 samples are collected at regular time intervals and urine
osmolarity is measured by osmometer. The increases in
15 osmolarity from the basal level are the pharmacodynamic
responses to the vasopressin transdermally absorbed.

20 The results demonstrate that when the skin is treated
with transdermal periodic iontophoretic system (TPIS) at
current density of 0.22 mA/cm₂, frequency of 2 KHz, on/off
25 ratio of 1/1, and square waveform for 40 min., the urine
osmolarity increases from the basal levels more rapidly and
substantially than with transdermal iontophoretic delivery
30 (TIDD) under the same experimental conditions (FIG. 28).

35 Example 19

An aqueous buffer solution of vasopressin (50 mcg/ml
containing 1.7 mCi/ml H₃-vasopressin) is prepared in
40 citrate-phosphate buffer at pH 7.4 with varying ionic
strengths. An aliquot of 3.5 ml of this vasopressin solu-
45 tion is filled into the refillable dosage unit having a
microporous membrane as the drug-releasing surface. The
dosage unit is then assembled as a part of the pharmaceuti-
50 cal reservoir electrode of the iontotherapeutic device and
membrane surface thereof is applied to the stratum corneum
55 side of hairless rat skin mounted in the Valia-Chien skin
permeation cell at 37°C. Samples are withdrawn at regular

time intervals and radioactivity is measured by scintillation counter to determine the amount of vasopressin which has been transdermally absorbed. The results demonstrate that vasopressin permeates through the hairless rat skin at constant, but slow rate for 30 hours (1.32 ± 0.38 ng/cm₂/hr). When the skin is treated with transdermal periodic iontophoretic system (TPIS) at current intensity of 1 mA, frequency of 2 KHz, on/off ratio of 1/1, and at the rate of 10 min. per 40 min. for 4 hours, the skin permeation profiles are enhanced with rate increases from $1.32 (\pm 0.38)$ ng/cm₂/hr (referred to as "passive diffusion") to the range of $65.9 (\pm 13.1)$ to $632 (\pm 65.0)$ ng/cm₂/hr, depending upon the ionic strength of vasopressin solution. The results of the experiment are shown in the following Table IX.

Table IX: Effect of Ionic Strength on Skin Permeation Rate of Vasopressin

<u>Ionic Strength</u>	<u>Skin Permeation Rate₁</u> (ng/cm ₂ /hr \pm SD)	<u>Enhancement Factor₂</u>
0.488	65.9 (\pm 13.1)	49.9 (\pm 18.0)
0.244	101.4 (\pm 9.1)	76.8 (\pm 6.9)
0.122	244.6 (\pm 26.3)	185.3 (\pm 19.9)
0.061	632.6 (\pm 65.0)	472.8 (\pm 59.0)

₁) The rates determined in the activation phase with lag time ranging from 0.48 (\pm 0.21) to 0.86 (\pm 0.15) hrs.

₂) Compared to the skin permeation rate of vasopressin by passive diffusion (1.32 ng/cm₂/hr).

5

10 The TPIS-facilitated skin permeation rate appears to be
dependent upon the ionic strength of drug solution. The
lower the ionic strength, the higher the rate of skin per-
meation and the greater the enhancement in skin permeability
15 (FIG. 29).

Example 20

20

An aqueous buffered solution of vasopressin (50 mcg/ml
containing 1.7 mCi/ml H_3 -vasopressin) is prepared in
25 citrate-phosphate buffer at pH 5.0 at ionic strength of
0.064. An aliquot of 3.5 ml of this vasopressin solution is
filled into the refillable dosage unit having a microporous
30 membrane as the drug-releasing surface. The dosage unit is
then assembled as a part of the pharmaceutical reservoir
electrode of the iontotherapeutic device and membrane sur-
35 face thereof is applied to the stratum corneum side of hair-
less rat skin mounted in the Valia-Chien skin permeation
40 cell at 37°C. Samples are withdrawn at regular time inter-
vals and radioactivity is measured by scintillation counter
45 to determine the amount of vasopressin which has been trans-
dermally absorbed.

50

The results demonstrate that vasopressin permeates
through the hairless rat skin at constant, but slow rate for
30 hours (0.98 ± 0.26 ng/cm₂/hr).

55

5 When the skin is treated with transdermal periodic
iontophoretic system (TPIS) at current intensity of 0.3 mA
10 frequency of 16 KHz, on/off ratio of 1/1, for 60 min., the
skin permeation profiles are enhanced with rate increases
from 0.98 (\pm 0.26) ng/cm₂/hr referred to as "passive dif-
15 fusion") to 757.3 (\pm 53.2) ng/cm₂/hr (FIG. 28), while the
duration of time lag is reduced from 9 hours down to 0.40 (\pm
20 0.06) hours). The data in FIG. 30 demonstrate the rever-
sibility of skin permeability that in less than 2 hours
after the TPIS treatment, the skin permeability returns to
25 the rate before the TPIS treatment. Then, TPIS can be
applied again to facilitate the skin permeation of vaso-
30 pressin.

5

What is Claimed is:

10

1. A lightweight, portable transdermal periodic ionto-
therapeutic device for transdermal administration of a
systemically-effective amount of an ionized pharmaceu-
tical, which is adapted to be worn by a subject being
iontotherapeutically treated, comprising

15

20

1) a DC power supply capable of providing an ionto-
therapeutically effective and physiologically
acceptable DC current in the range up to about
10mA;

25

30

2) a periodic waveform generator electrically con-
nected to the DC power supply and having inte-
grated circuitry capable of providing a) a
periodic waveform in the square, triangular, sinu-
soidal, trapezoidal, or other acceptable geometric
form or combination thereof; b) an on/off ratio of
1/50 to 10/1; and c) a repetition frequency from
about 10 Hz to about 50 KHz;

35

40

45

50

55

3) an output circuit electrically connected to said
waveform generator which a) can provide a periodic
DC current in a pre-selected waveform of said
forms; b) monitors current intensity delivered; c)
adjusts and maintains the current intensity within
predetermined maximum and minimum levels and d)
delivers the current to a reservoir electrode for

5

10

iontotherapeutic transdermal administration of
said peptide pharmaceutical;

15

20

25

30

35

40

45

50

55

- 4) a pharmaceutical reservoir electrode which can be
preselected to be either the cathode or the anode
depending upon whether the ionized pharmaceutical
is anionic or cationic; said electrode having a
receptacle adapted to receive a unit dose of said
peptide pharmaceutical in which said peptide is in
aqueous solution at a pH at least 1.0 pH unit
below or above the isoelectric point of said pep-
tide; said electrode with said received unit dose
adapted to be placed in electrical contact with
the intact skin to be treated iontotherapeuti-
cally; said electrode having a terminal to receive
and to transmit through said unit dose the said
periodic DC current and said unit dose adapted to
be in electrical contact with said terminal;

- 5) receptor electrode adapted to be in electrical
contact with the intact skin to be treated and
forming with said pharmaceutical reservoir elec-
trode a combination of anode and cathode elec-
trodes;

said electrodes electrically connected to said
output circuit and providing when placed upon the

5 skin of a subject being treated a current path
through the intervening tissue of the subject
10 being treated; and

6) a preprogramable control element electrically
15 integrated within said device to preprogram and to
control said iontotherapeutic administration on an
automated basis as in accordance with a physi-
20 cian's prescription entered into the control ele-
ment, without interaction of a subject being
treated with said device for the administration
25 except to permit said subject to stop operation of
the device as in the event of an emergency.

30 2. A device of Claim 1 which has electrically connected
with the control element thereof a sensor.

35 3. A device of Claim 2 wherein the sensor senses a level
of a physiological entity in the body of the subject
40 which correlates with the pharmaceutical being admin-
istered iontothereapeutically and signals said informa-
tion to said control element.

45 4. A device of Claim 2 wherein the sensor senses a pre-
determined skin condition of the body of the subject
50 and signals the information to said control element.

- 5 5. A device of Claim 1 wherein the device interfaces with
 a computer system to enter into the control element
10 thereof a preprogrammed prescription and other instruc-
 tions or to receive data on the functioning of the
 device.
- 15 6. A device of Claim 1 wherein the device is a wrist-band
 type.
- 20 7. A transdermal periodic iontotherapeutic process for
 administering a controlled and systemically effective
25 amount of an ionized pharmaceutical which is stable for
 transdermal administration and is transdermally absorb-
30 able using a device as defined in Claim 1, by
- 1) entering a prescription or other instructions for
35 administering said pharmaceutical into the control
 element of said device;
- 40 2) assembling a dosage unit containing a pharmaceuti-
 cally acceptable aqueous solution of said ionized
 pharmaceutical into a receptacle of a reservoir
45 electrode of said device, which electrode is a
 cathode or anode depending upon whether said
50 ionized peptide is anionic or cationic, said solu-
 tion having a pH at least about 1.0 pH unit below
 or above the isoelectric or pKa point of said
55 pharmaceutical;

5 3) placing the cathode and anode electrodes of said
transdermal periodic iontotherapeutic system in
10 electrical contact with the intact skin to be
treated;

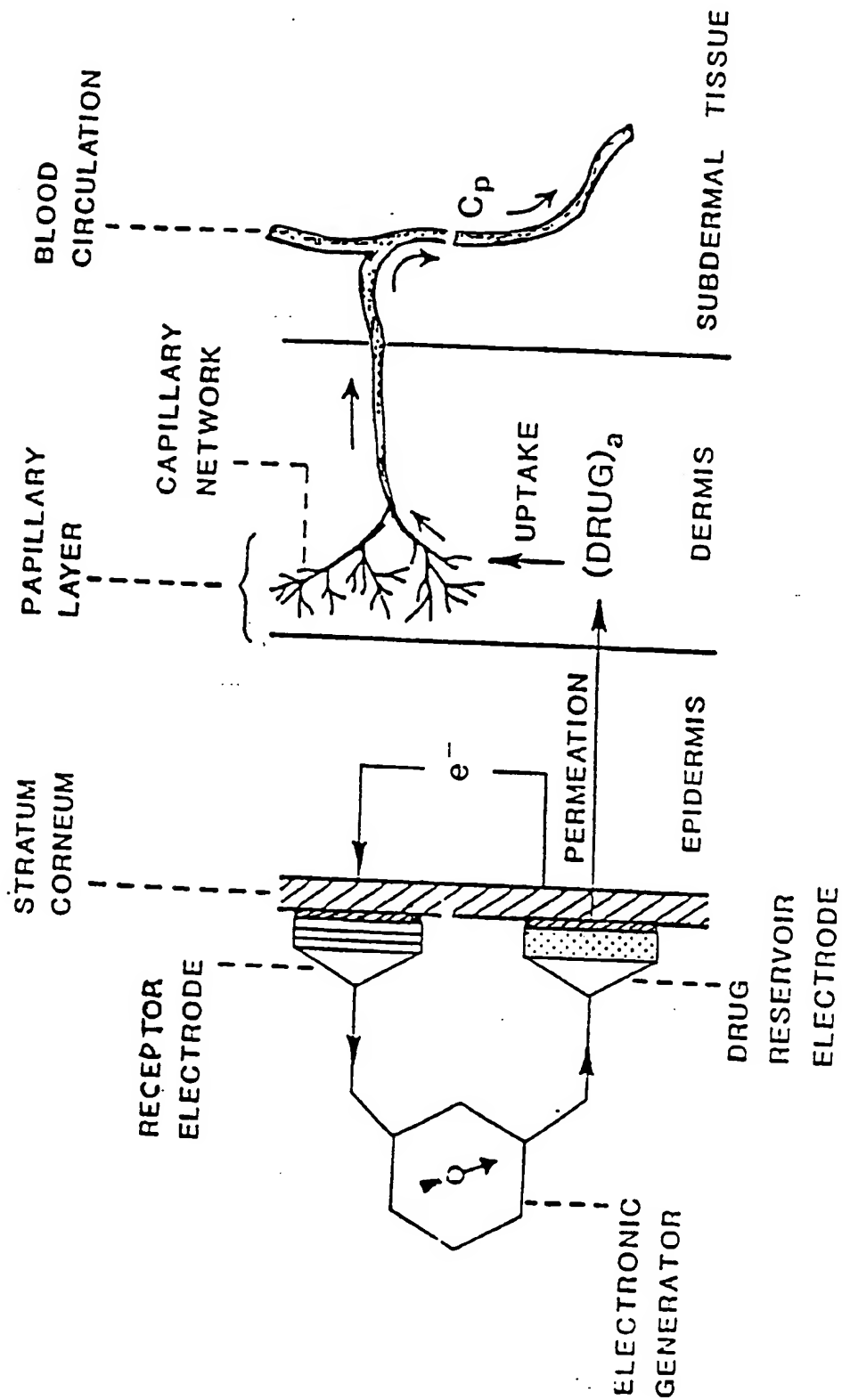
15 4) applying upon command of said control element an
iontotherapeutically effective, periodic DC cur-
rent of up to about 10 mA based on a reservoir
20 electrode/skin-contacting area of about 5 cm²
using a) a periodic waveform in the square, tri-
25 angular, sinusoidal, trapezoidal, or other accept-
able geometric form, or combinations thereof, b) a
physiologically acceptable repetition frequency of
30 at least about 10 HZ, and c) an on/off ratio of
from 1/50 to 10/1; said process providing a sys-
35 temically effective absorption of said ionized
pharmaceutical from said solution at a rate of at
least 500 percent from that provided by passive
40 diffusion transdermal absorption from said solu-
tion during an administration time of at least 2
45 hours.

50 8. A process of Claim 7 wherein the ionized pharmaceutical
is an ionized peptide pharmaceutical.

- 5 9. A process of Claim 7 in which the pH of the pharmaceu-
 tical solution is at least about 1.5 pH units below or
10 above the isoelectric or pKa point of said pharmaceuti-
 cal.
- 15 10. A process of Claim 7 in which the pH of the pharmaceu-
 tical solution is at least about 2.0 pH units below or
20 above the isoelectric or pKa point of said pharmaceuti-
 cal.
- 25 11. A process of Claim 7 in which the pH of the pharmaceu-
 tical solution is at least about 1.5 or about 1.0 pH
30 units below the isoelectric or pKa point of said phar-
 maceutical.
- 35 12. A process of Claim 7 in which the ionized pharmaceuti-
 cal is insulin and the pH of the insulin solution is in
 the range of about pH 3.0 to pH 4.0.
- 40 13. A process of Claim 7 in which the pH of the insulin
 solution is about pH 3.6.
- 45 14. A process of Claim 7 in which the current intensity is
 not more than about 5 mA based on a reservoir elec-
50 trode/skin-contacting area of about 5 cm₂.
- 55 15. A process of Claim 7 in which the current intensity is
 not more than about 2 mA based on a reservoir elec-
 trode/skin-contacting area of about 5 cm₂.

- 5 16. A process of Claim 1 in which the current intensity is
not more than 1 mA based on a reservoir electrode skin-
10 contacting area of about 5 cm₂.
- 15 17. A process of Claim 7 wherein the solution is an insulin
solution having a pH which is at least about 1.5 pH
units lower or higher than the isoelectric point of the
20 insulin, the current intensity not more than about 2 mA
based on a reservoir electrode skin-contacting surface
area of about 5 cm₂, the administration times are not
25 more than about 40 minutes, and the repetition fre-
quency is at least about 1000 Hz.
- 30 18. A battery belt adapted to be worn around the wrist or
other part of a subject's body to power an electronic
device used by said subject, said device comprising
35 1) a band adapted to house batteries;
2) said batteries connected in series;
40 3) a terminal electrically connected with the series
of batteries adapted to connect electrically
through a connecting line with said electronic
45 device.
- 50 19. A battery belt of Claim 18 adapted for use with a
device of Claim 1.
- 55

FIG. 1



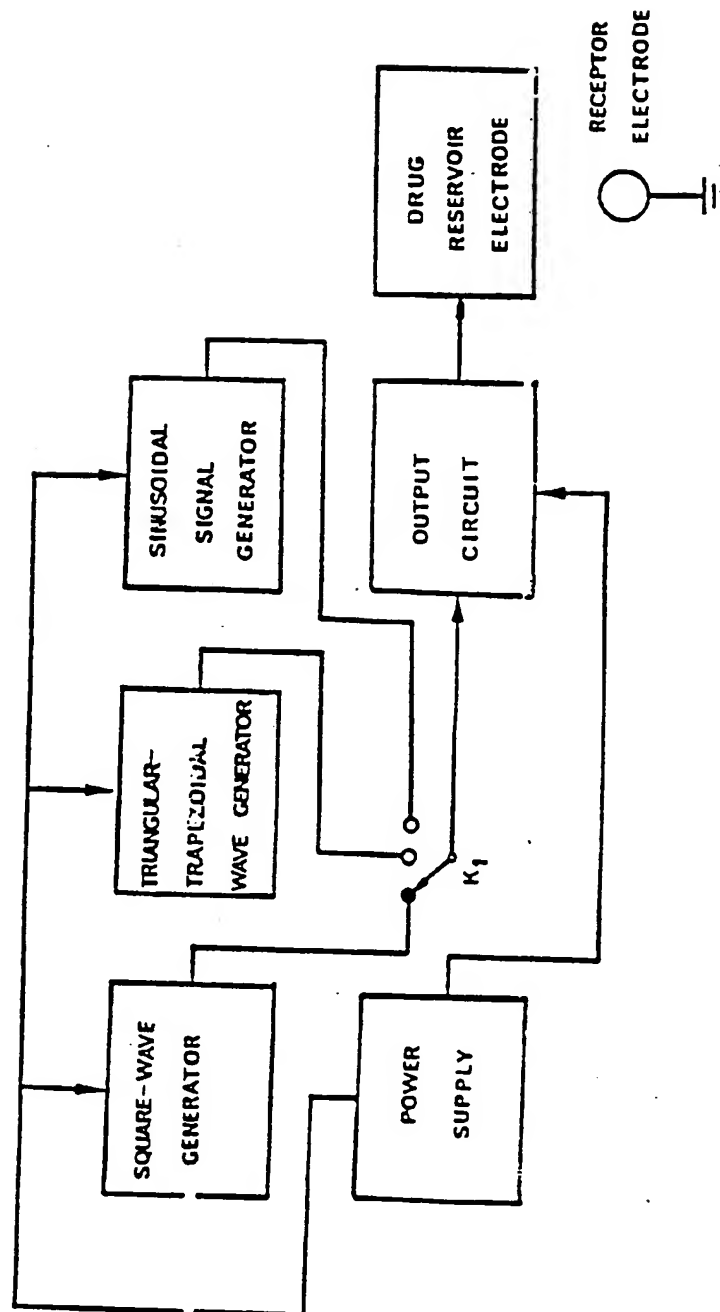


FIG. 2

3/31

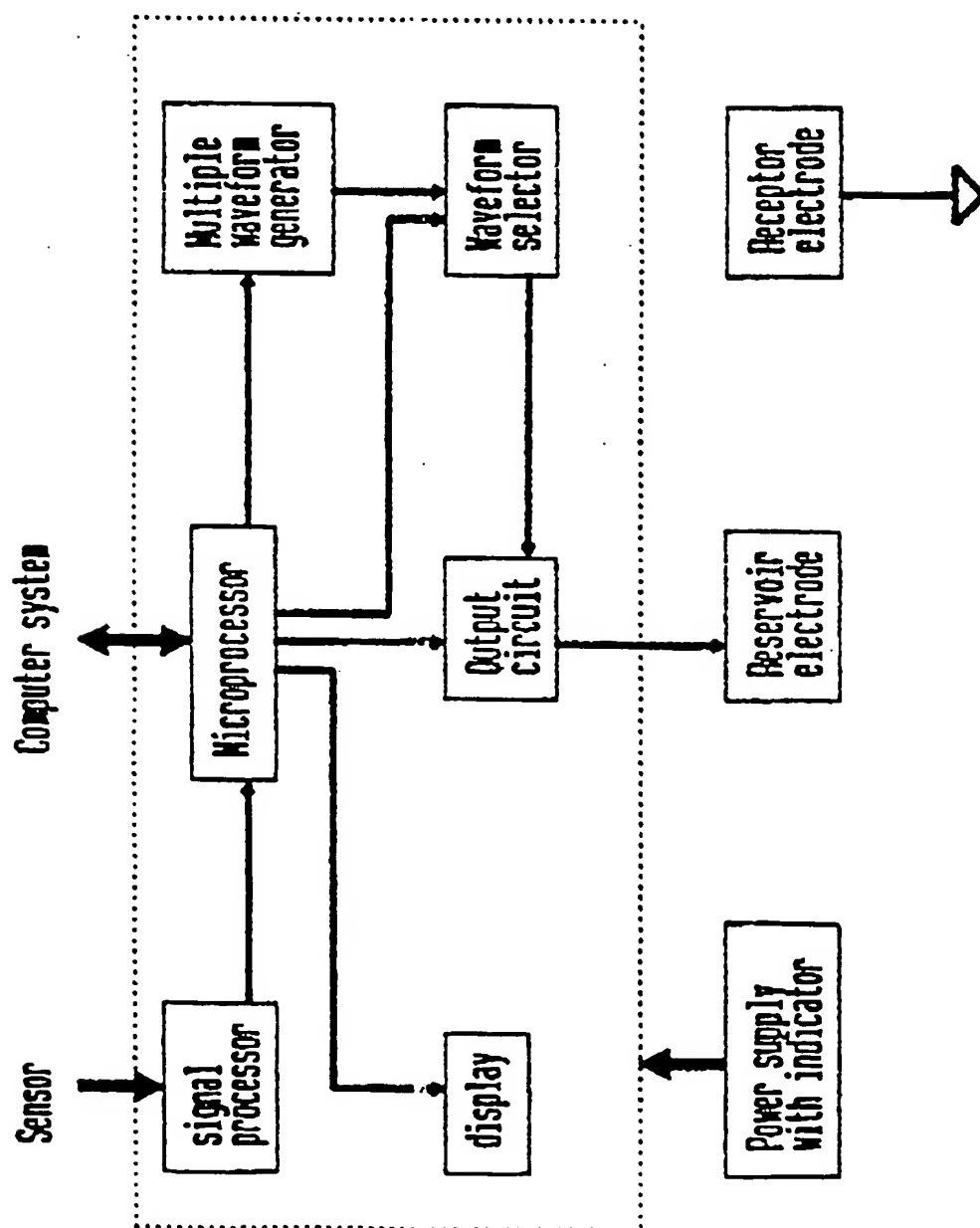


Fig. 3

4/31

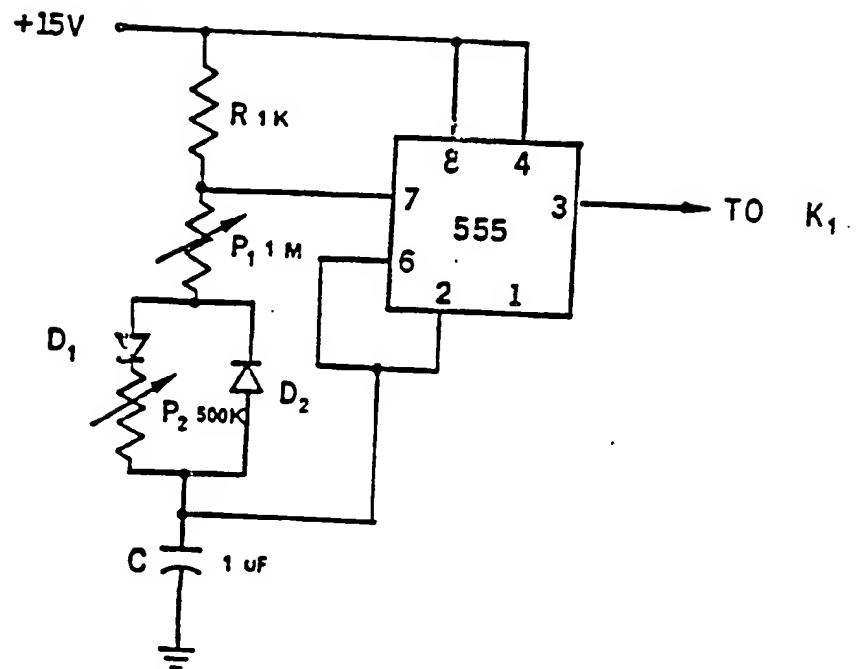


FIG. 4

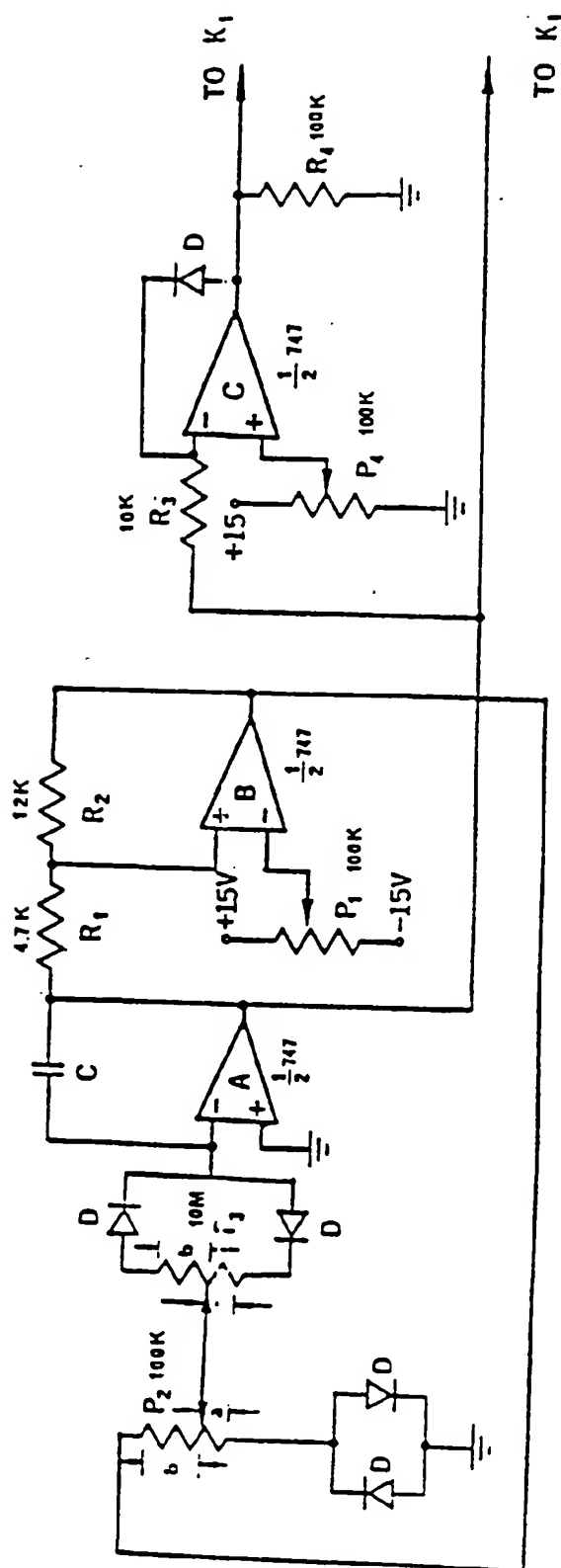


FIG. 5

6/31

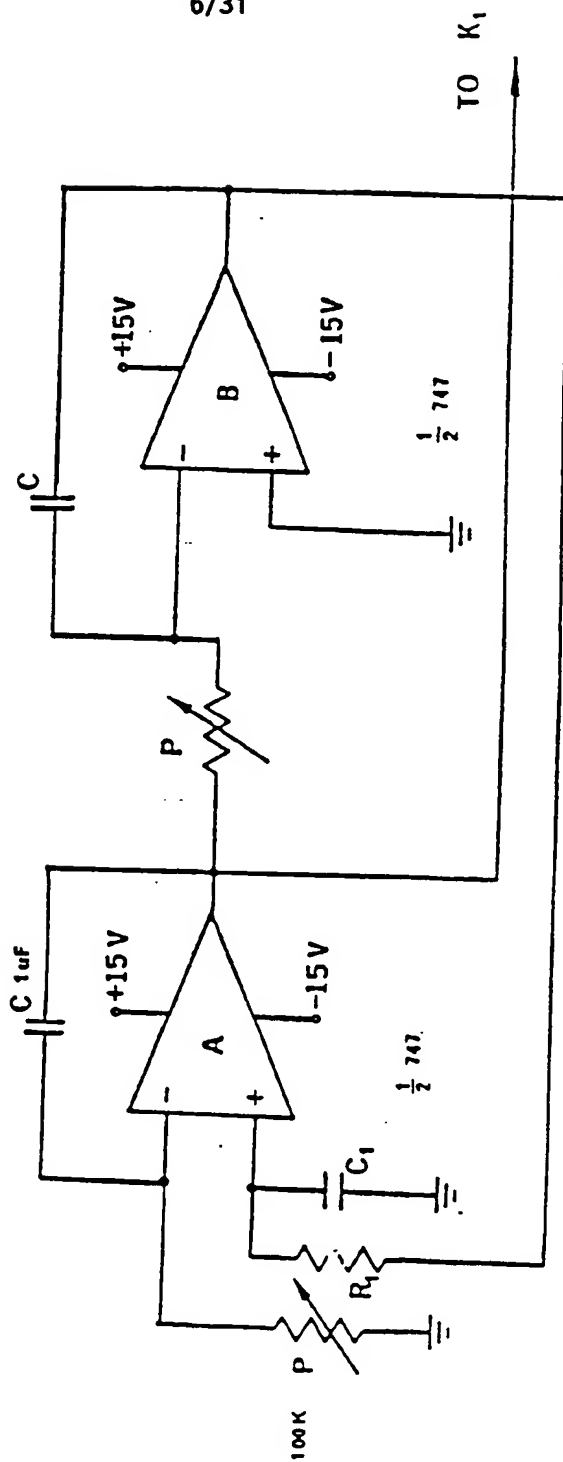
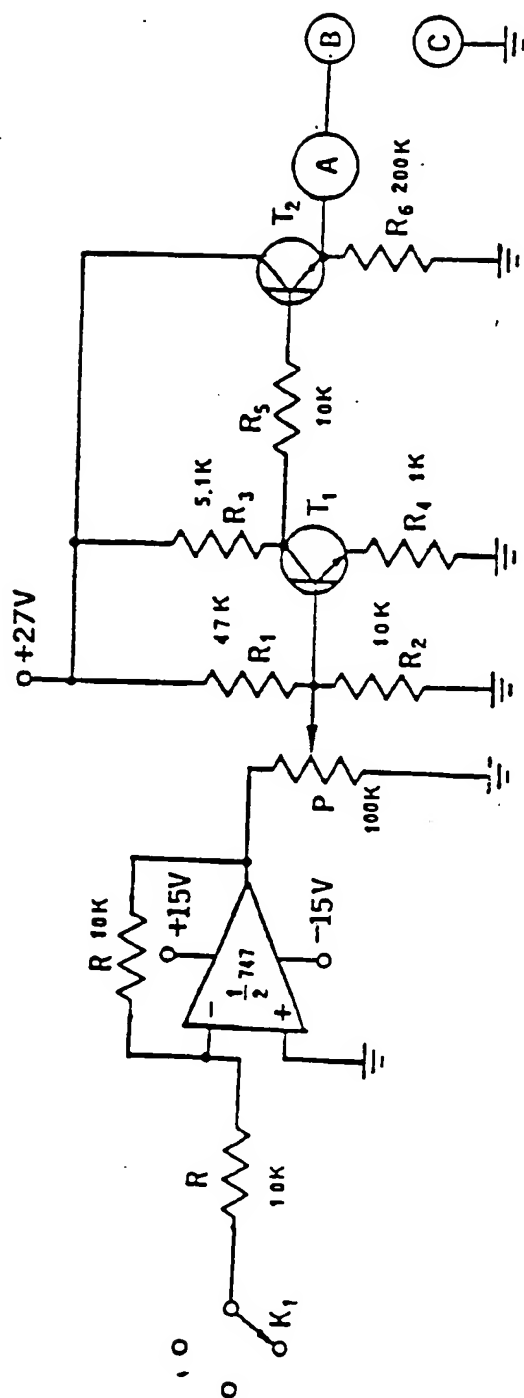


FIG. 6



F1G.7

8/31

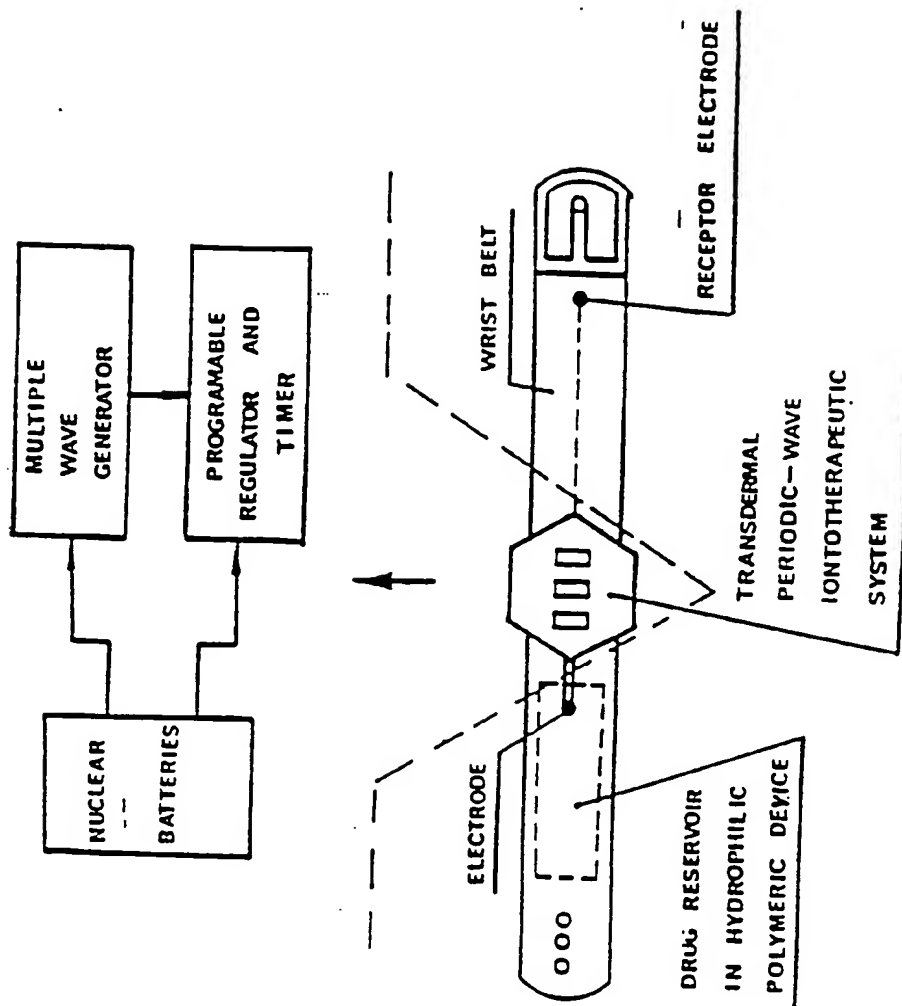


FIG. 8

9/31

TRANSDERMAL PERIODIC IONTO-THERAPEUTIC SYSTEM
(TPIS)

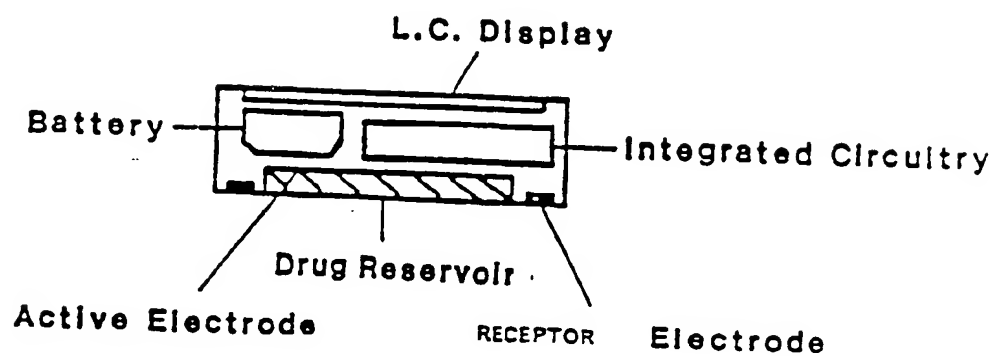


FIG. 9A

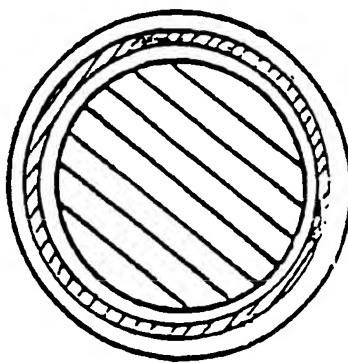


FIG. 9B

10/31

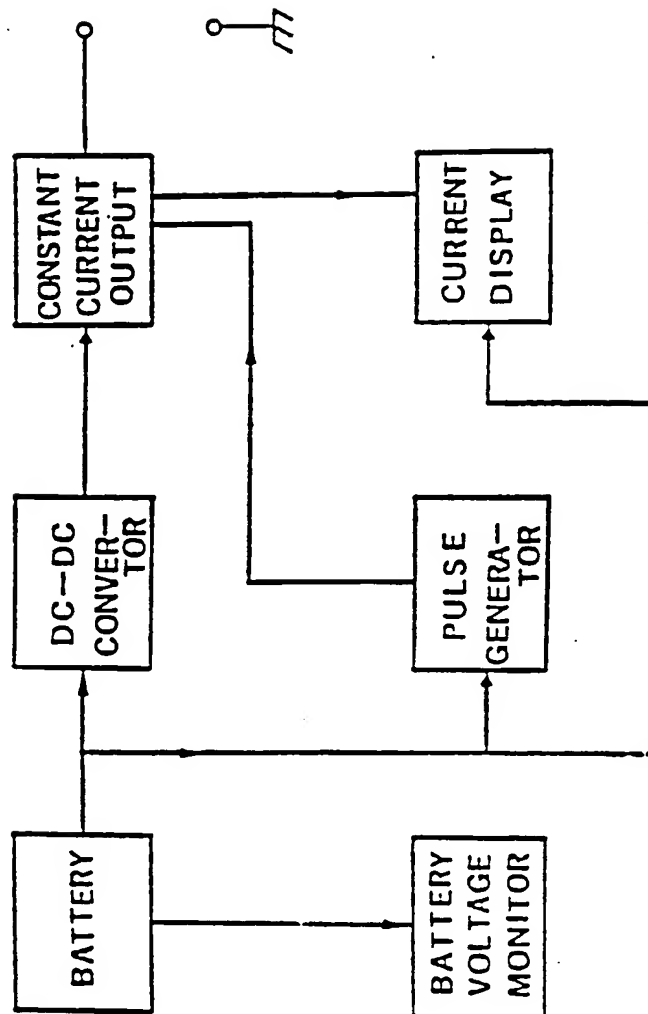


FIG. 10

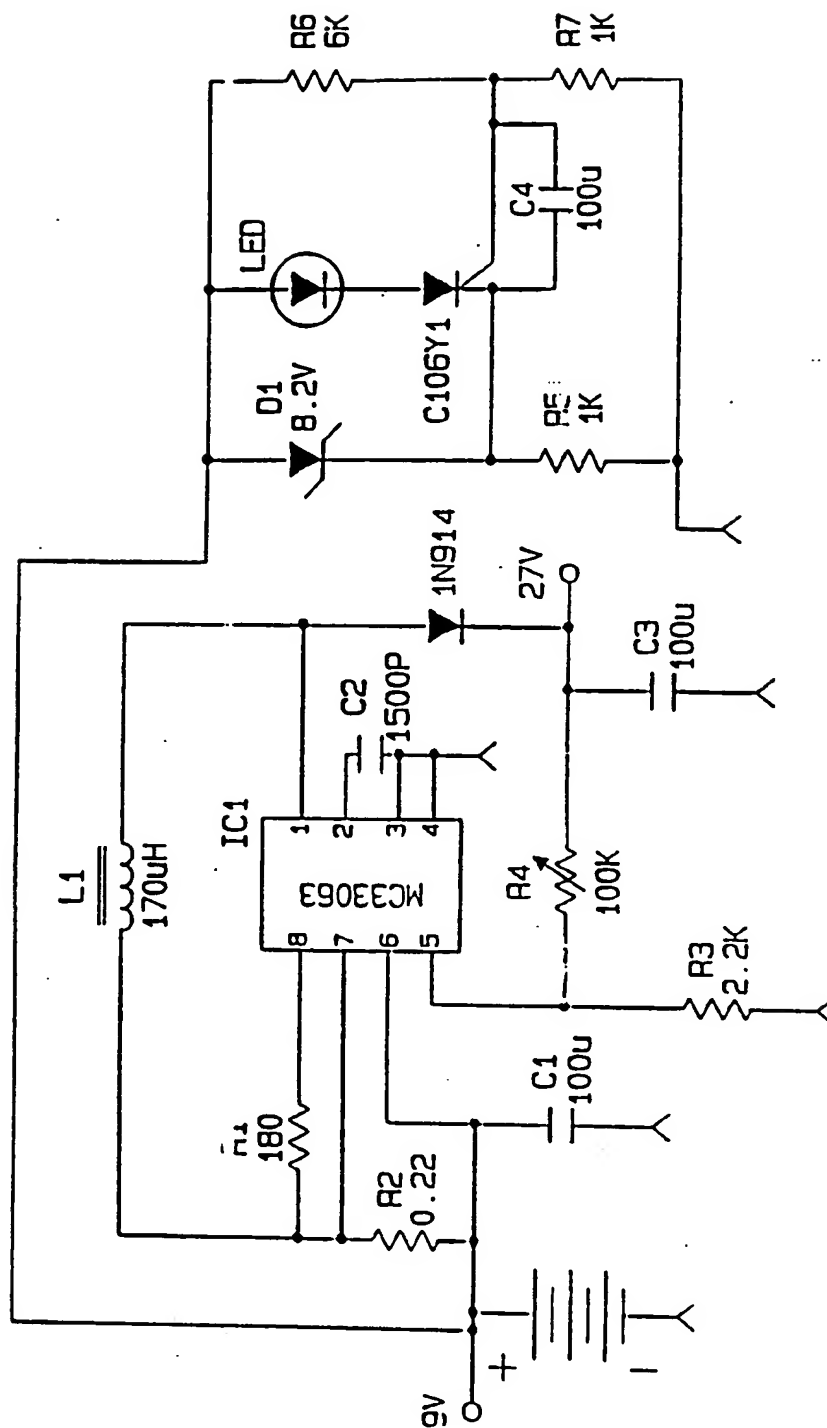
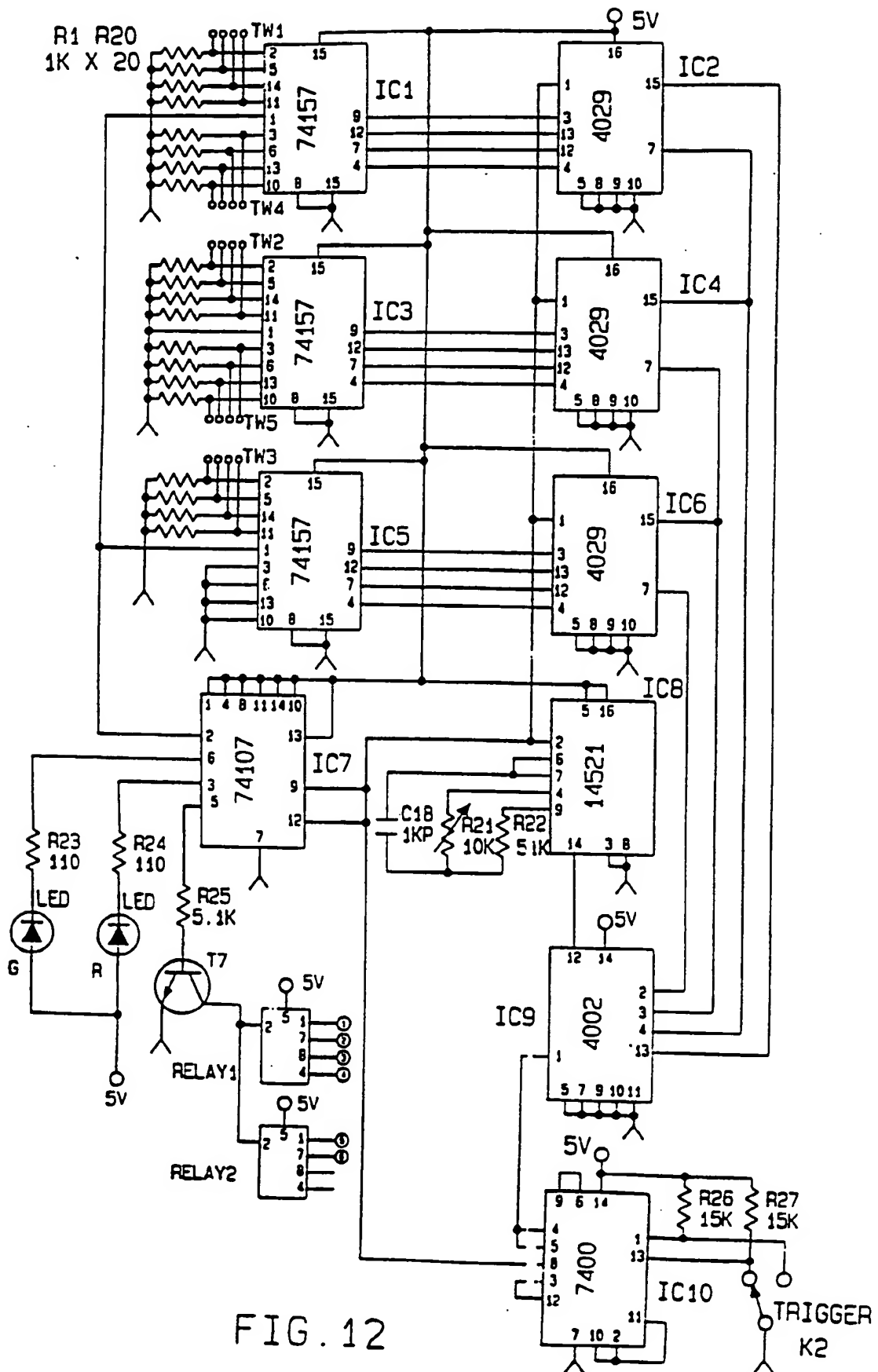


FIG. 11A



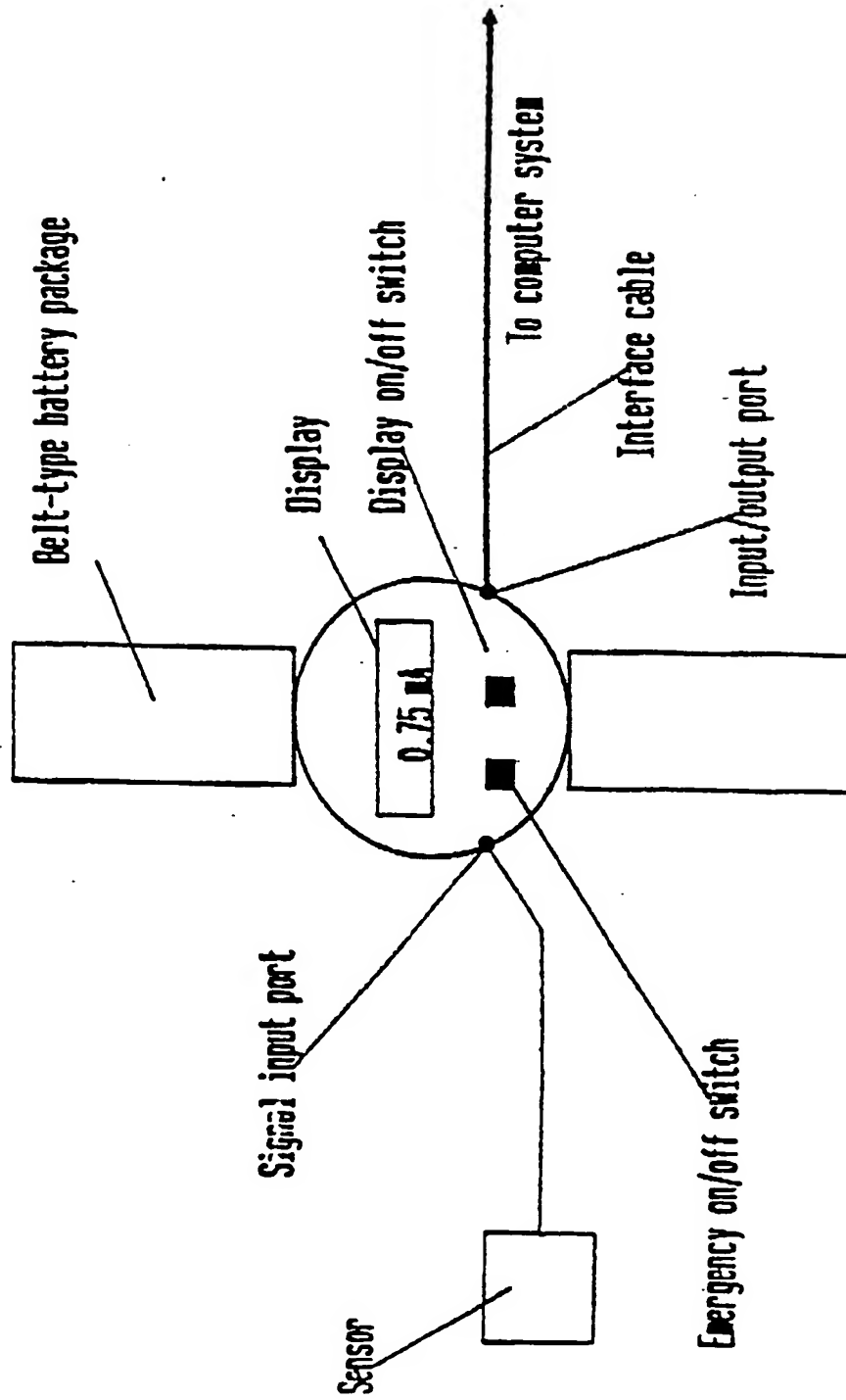


Fig. 13

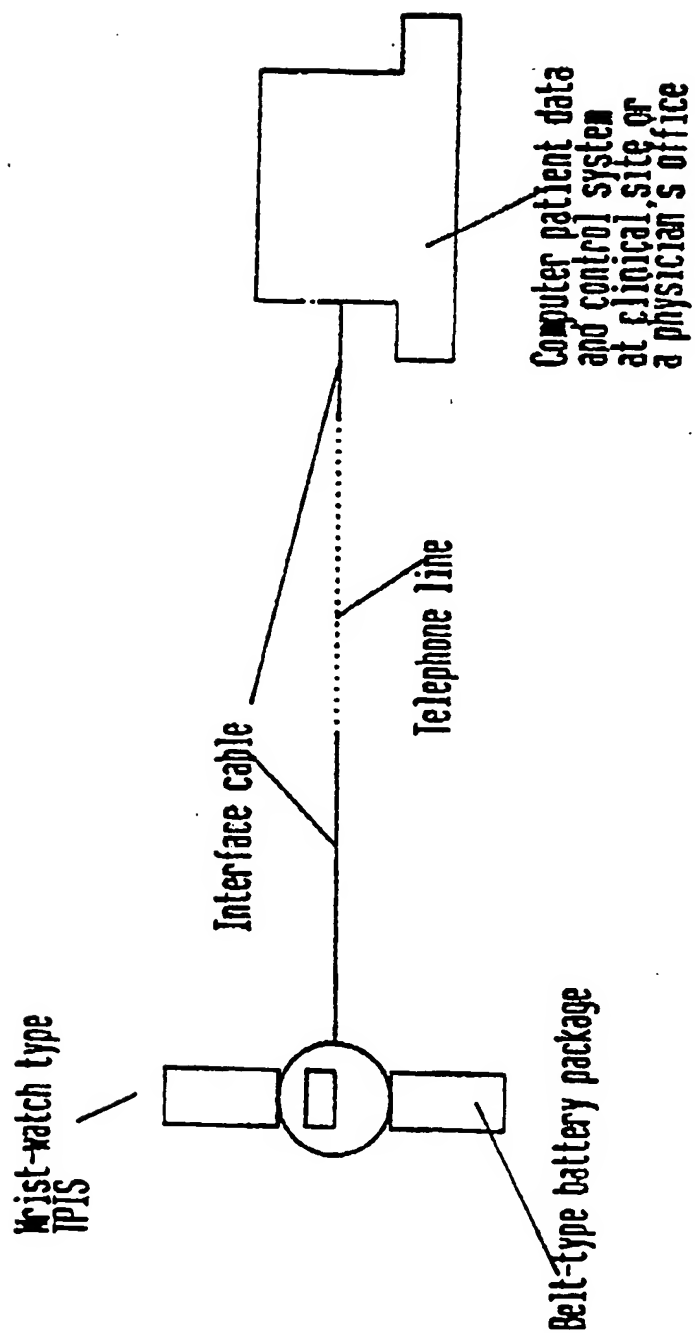


Fig. 14

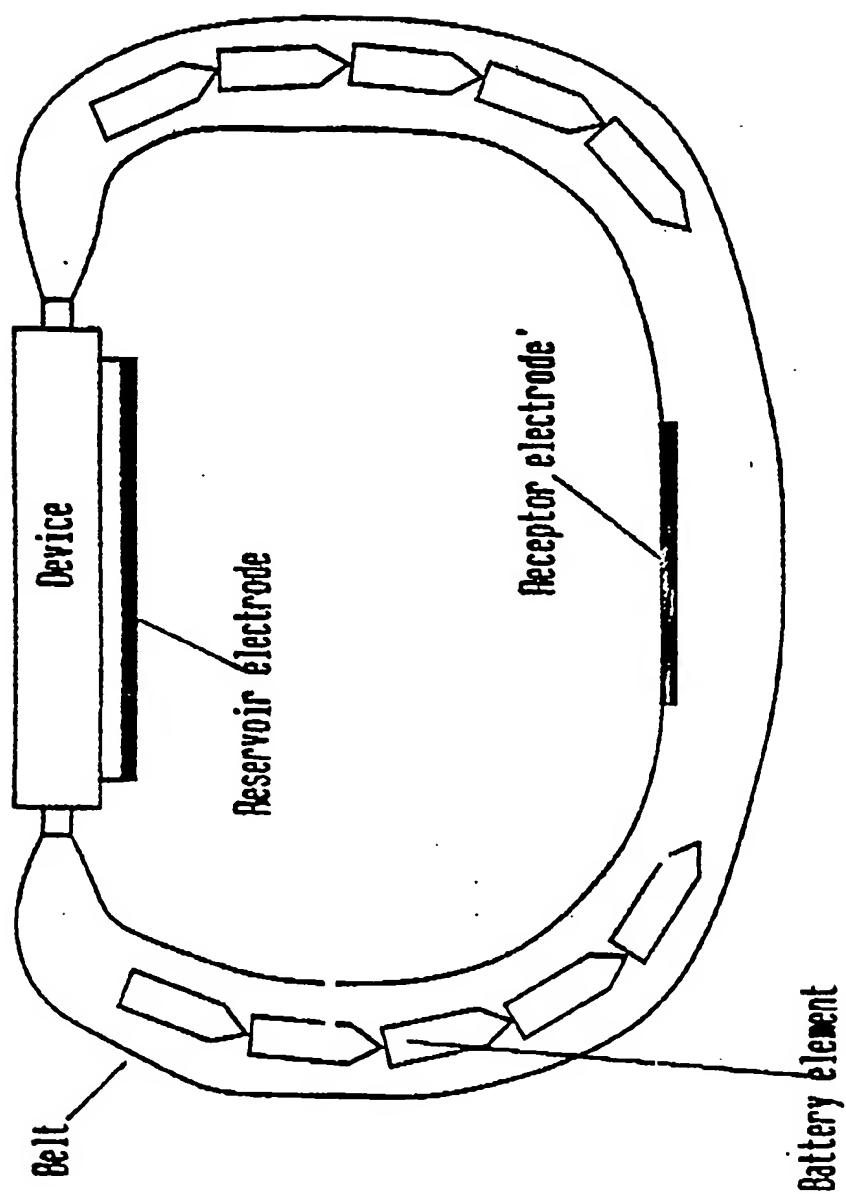


Fig. 15

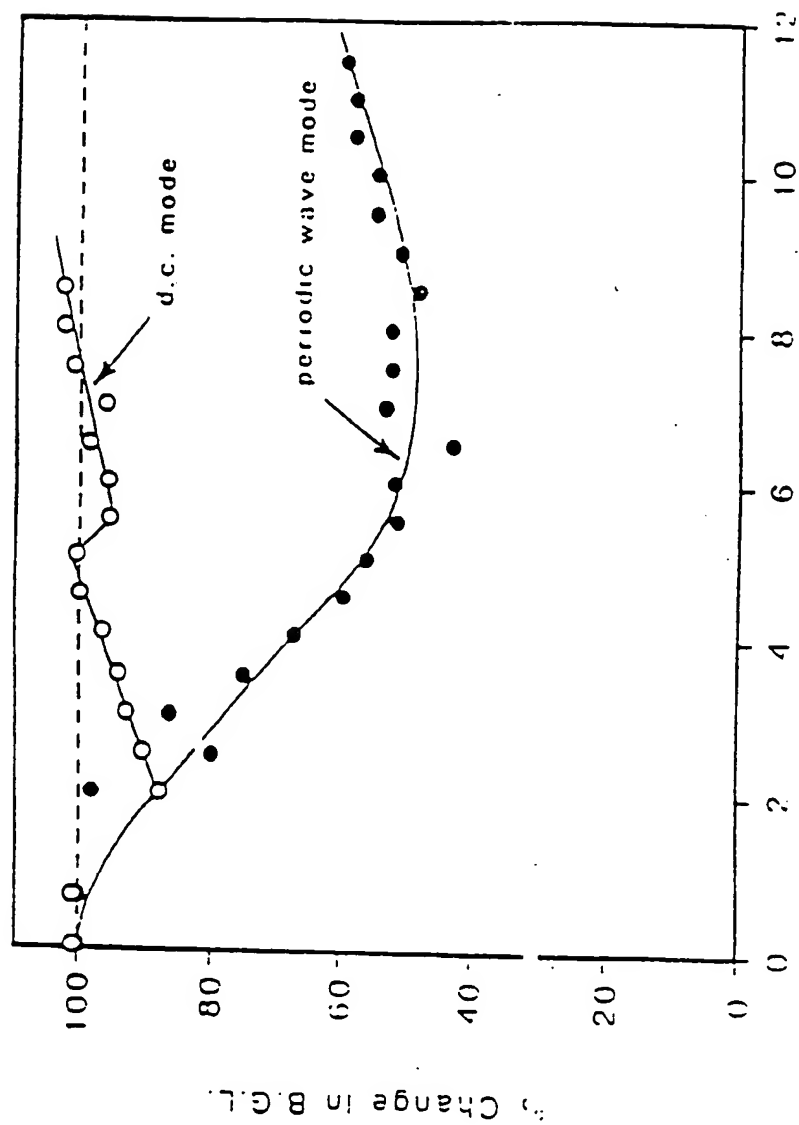


FIG. 16

18/31

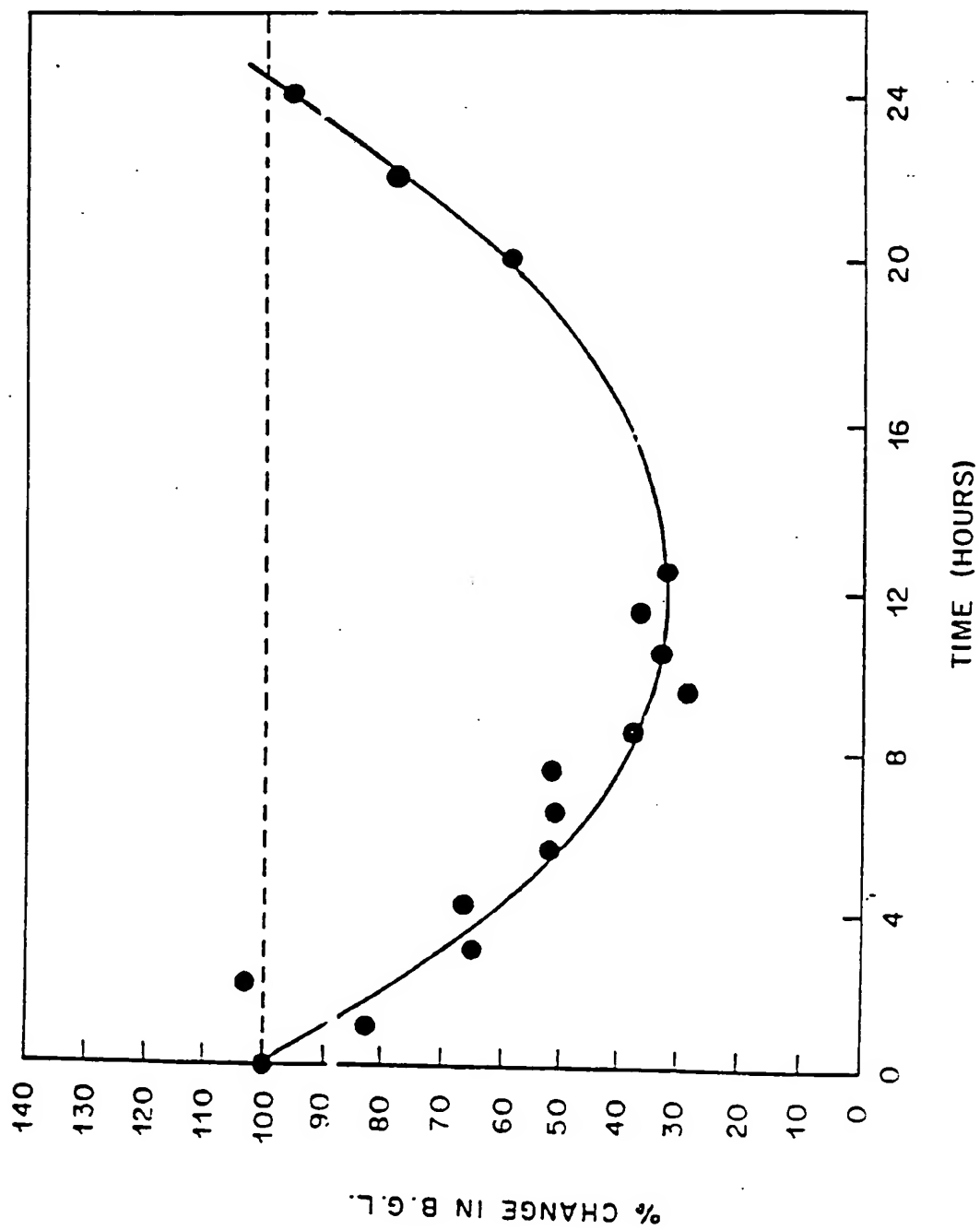
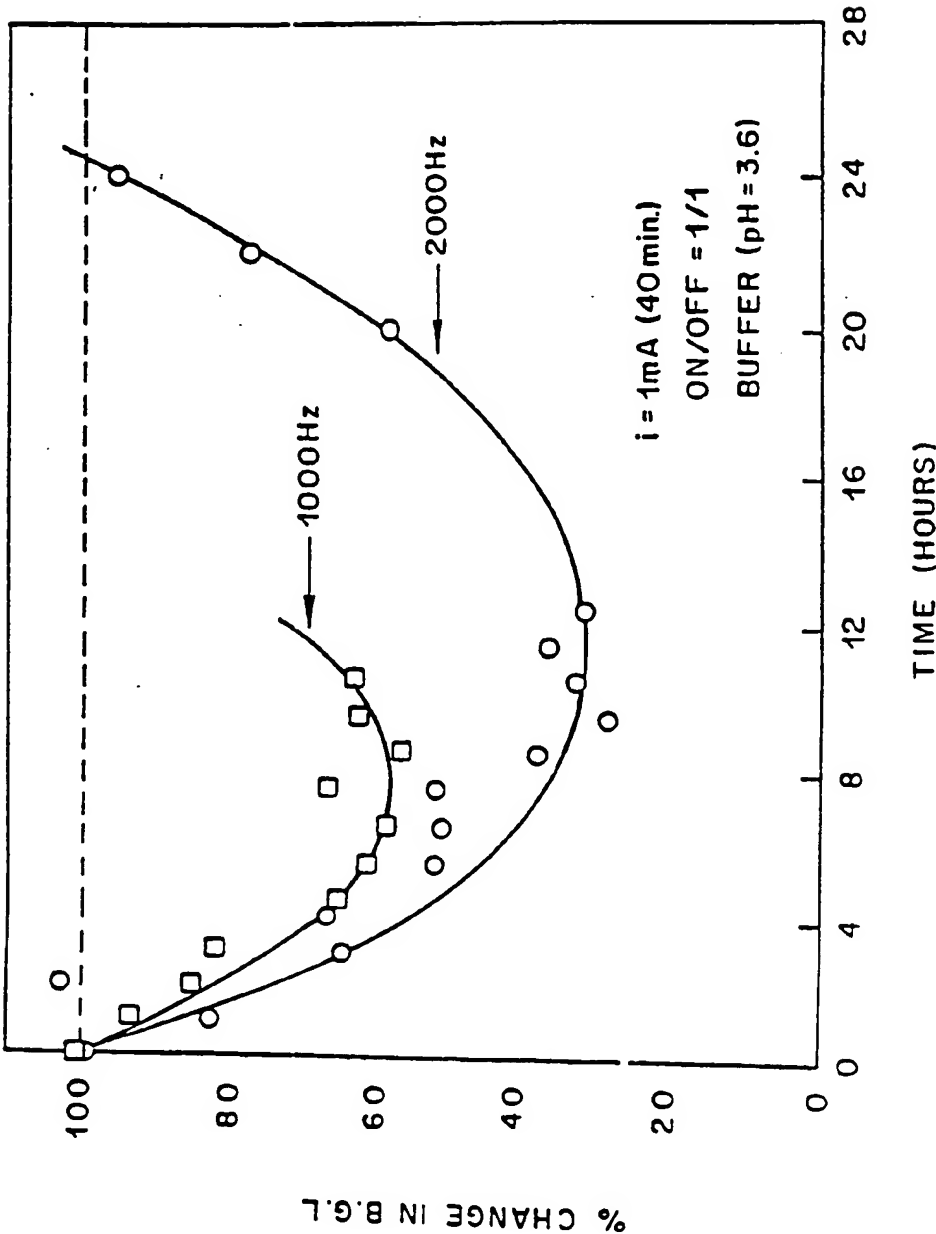
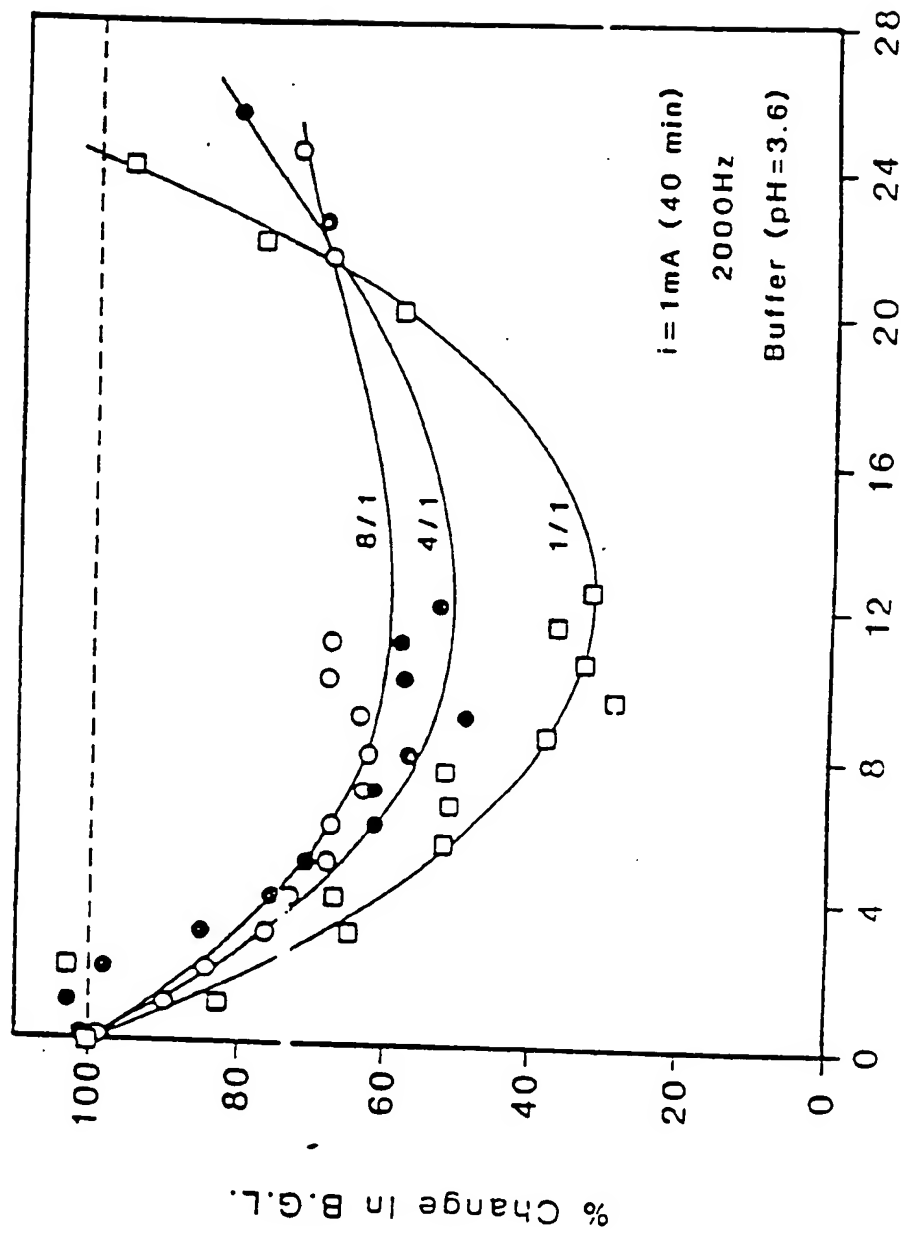


FIG. 17

FIG. 18



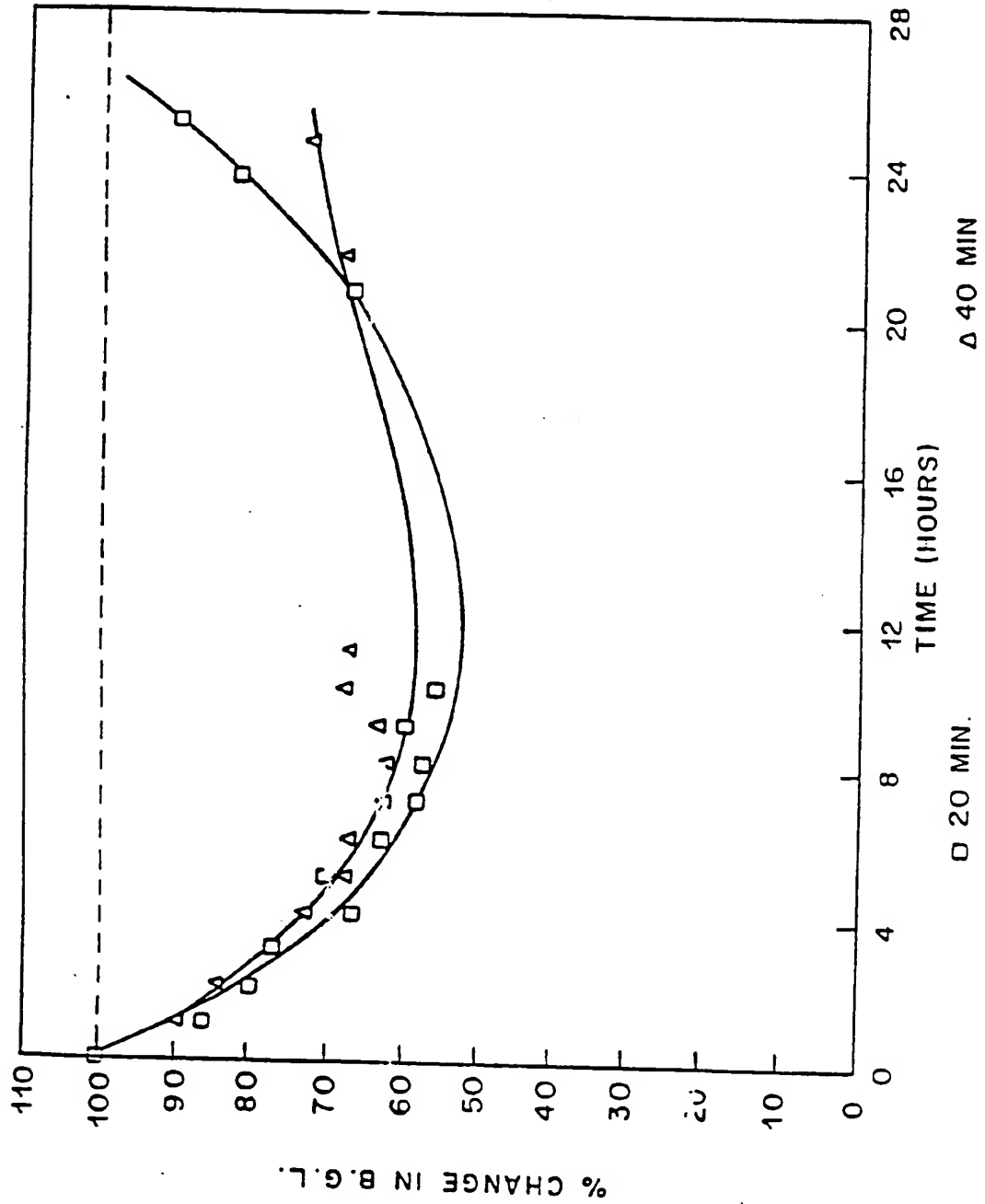
20/31



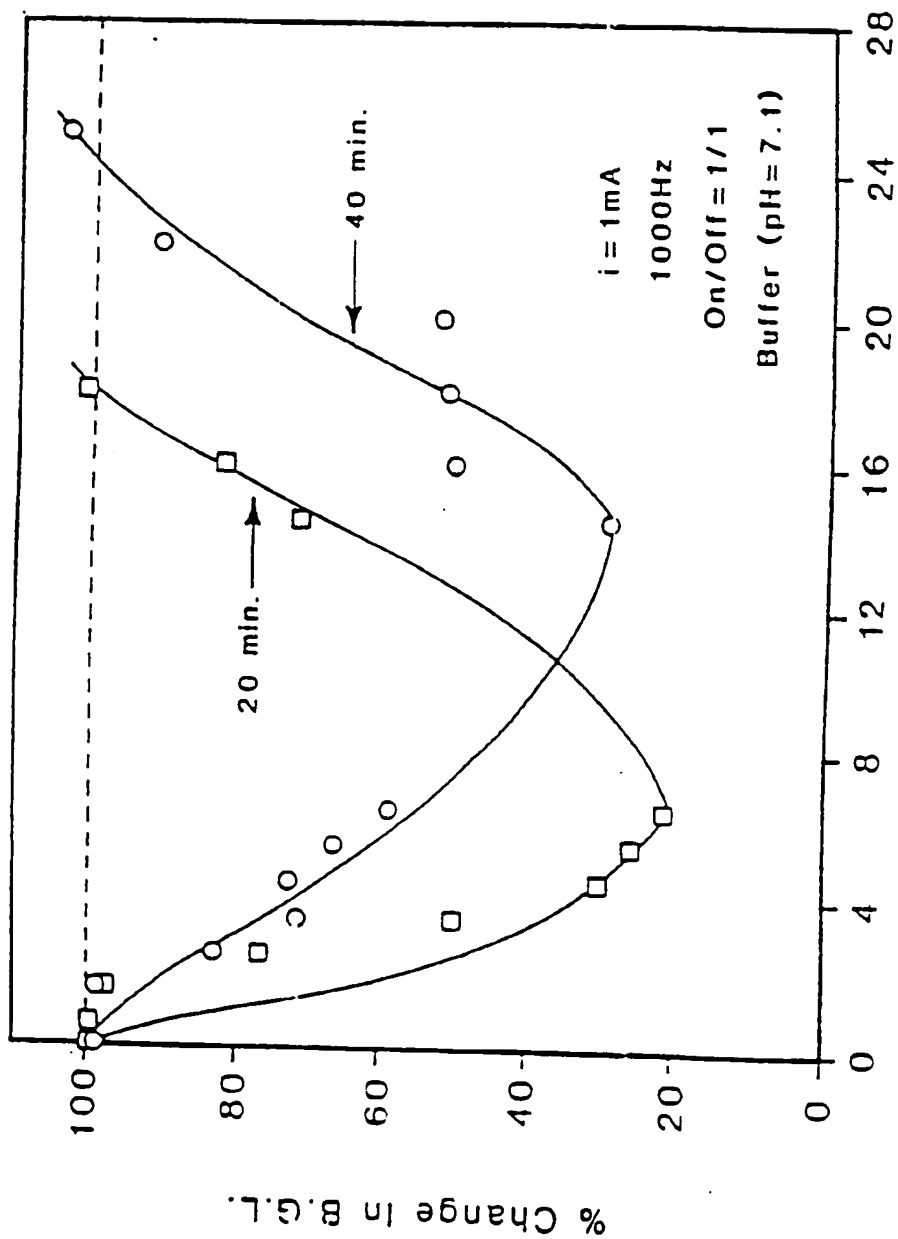
Time (hours) FIG. 19

21/31

FIG. 20



22/31



Time (hours) FIG. 21

23/31

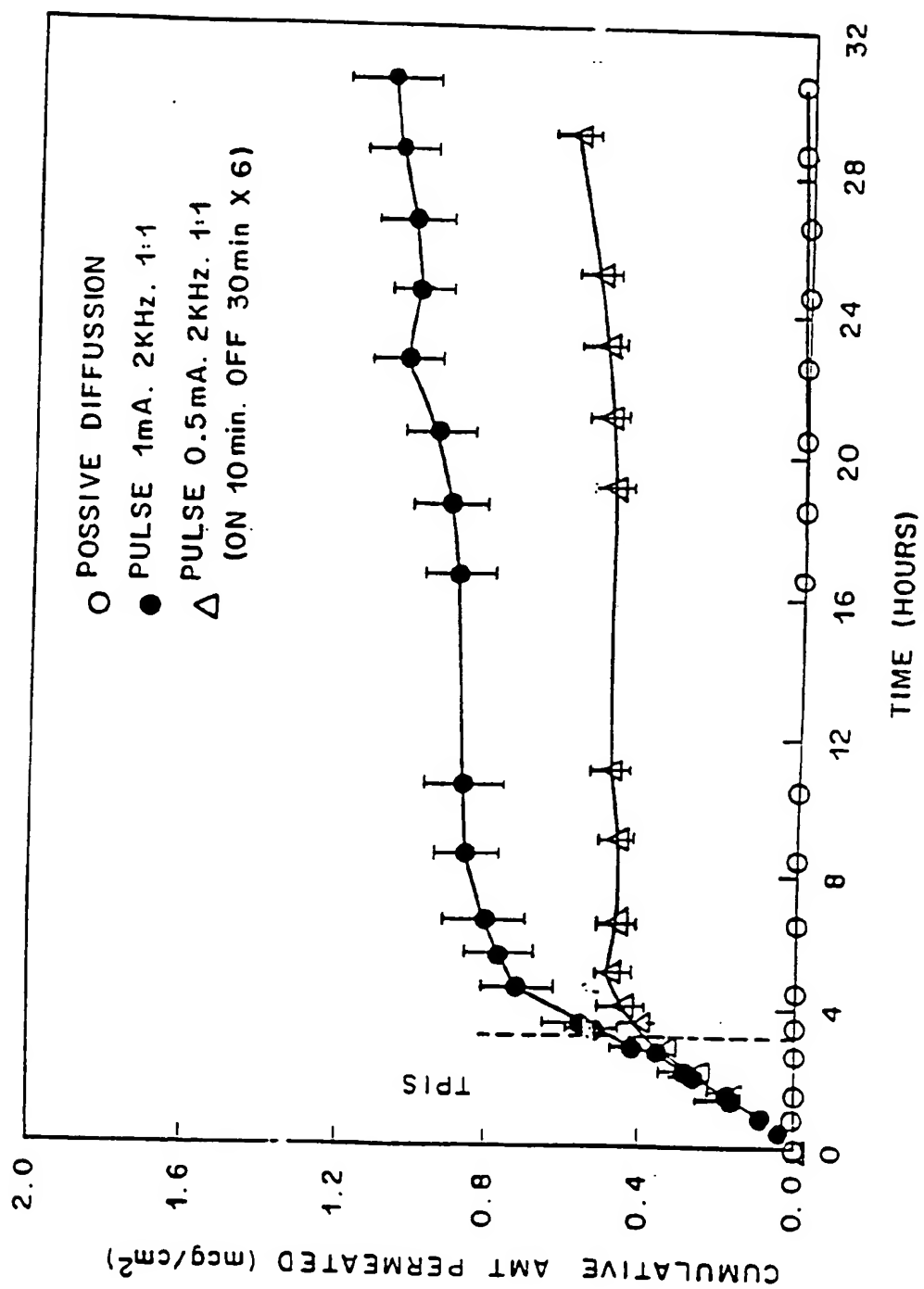
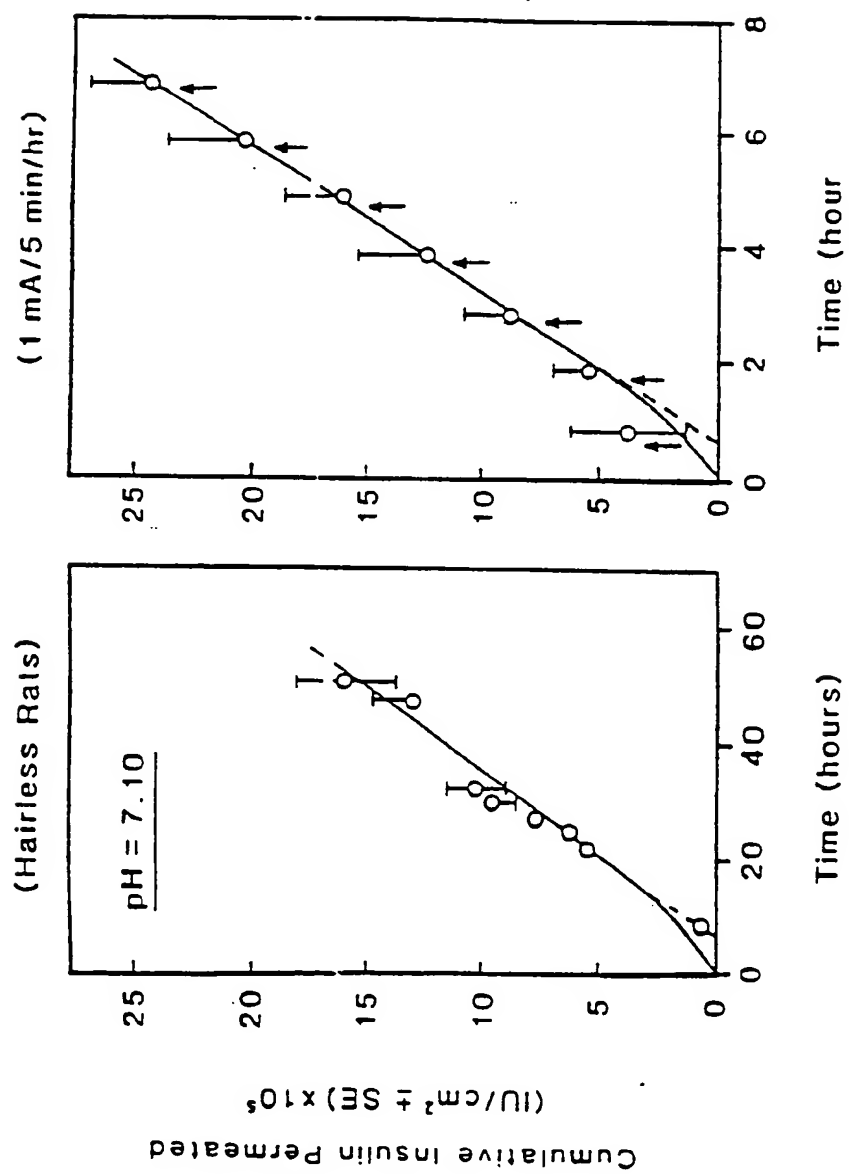


FIG. 22

24/31



25/31

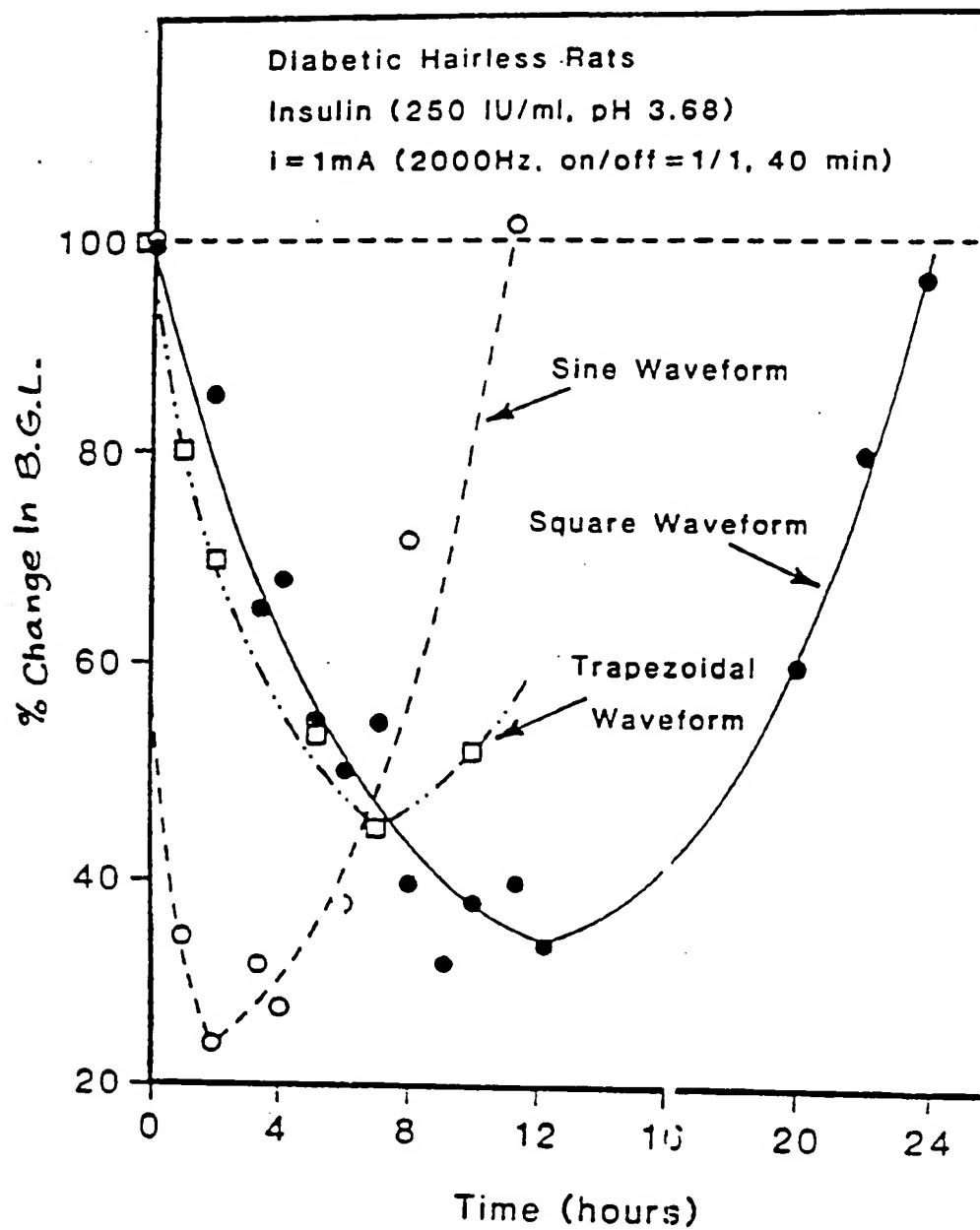


FIG. 24

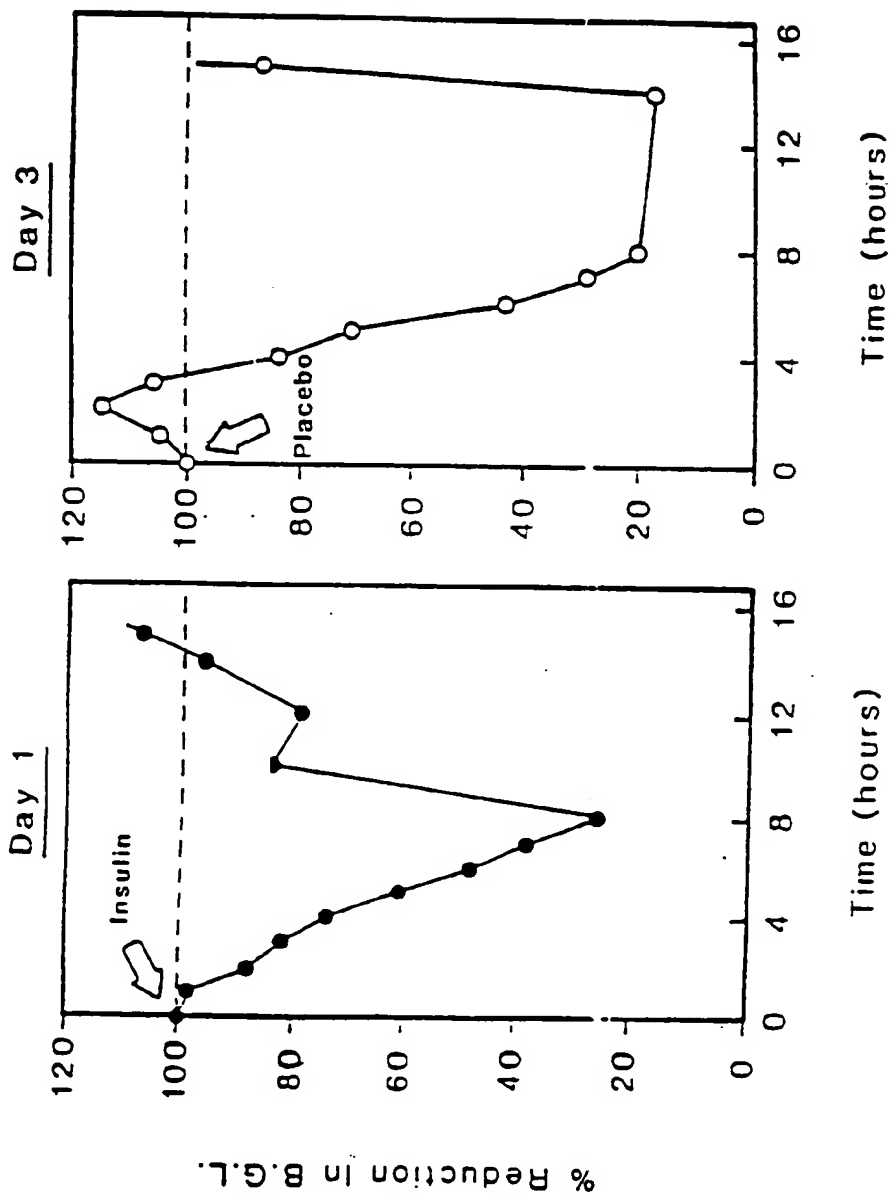


FIG. 25B

FIG. 25A

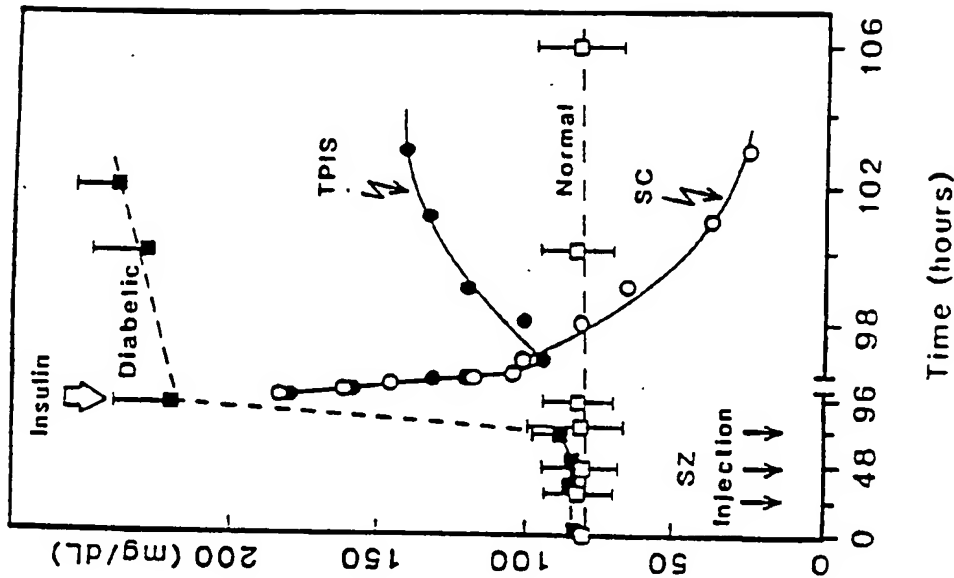


FIG. 26B

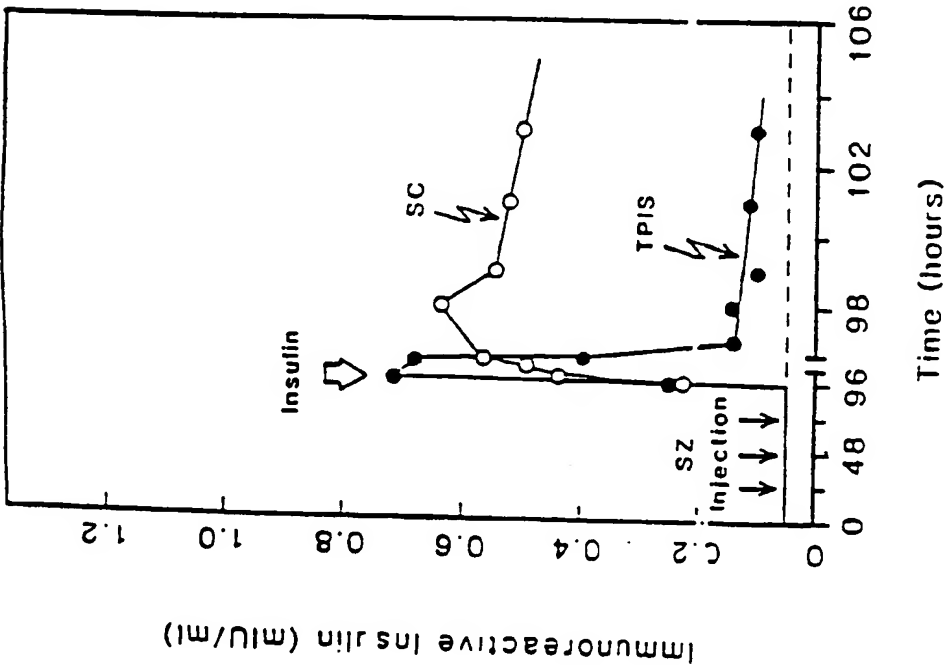


FIG. 26A

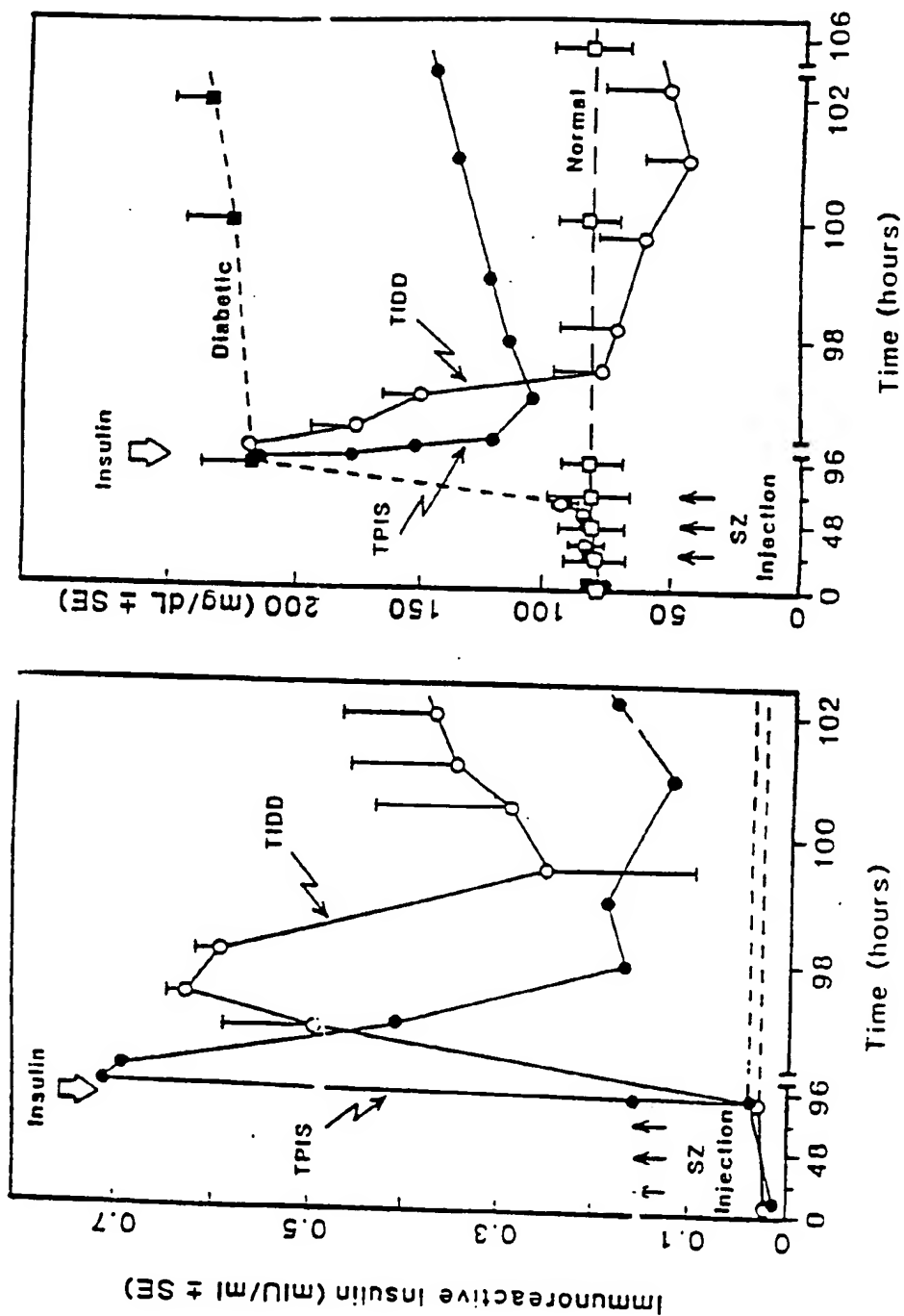


FIG. 27B

FIG. 27A

29/31

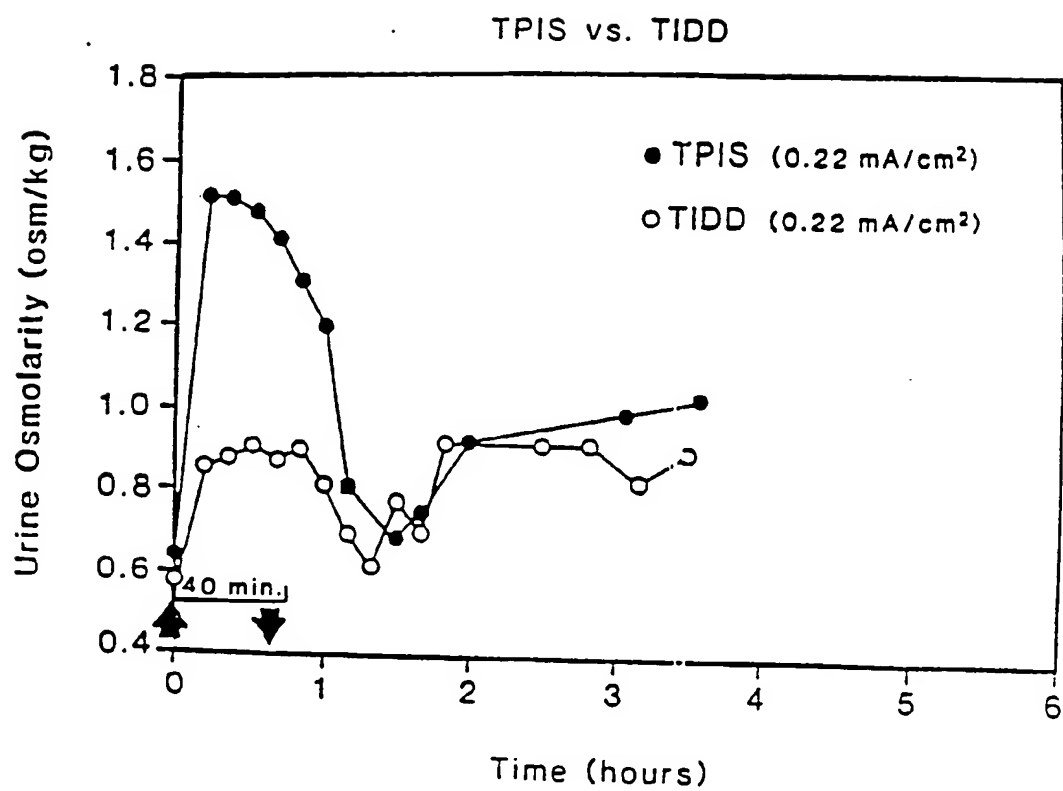


FIG. 28

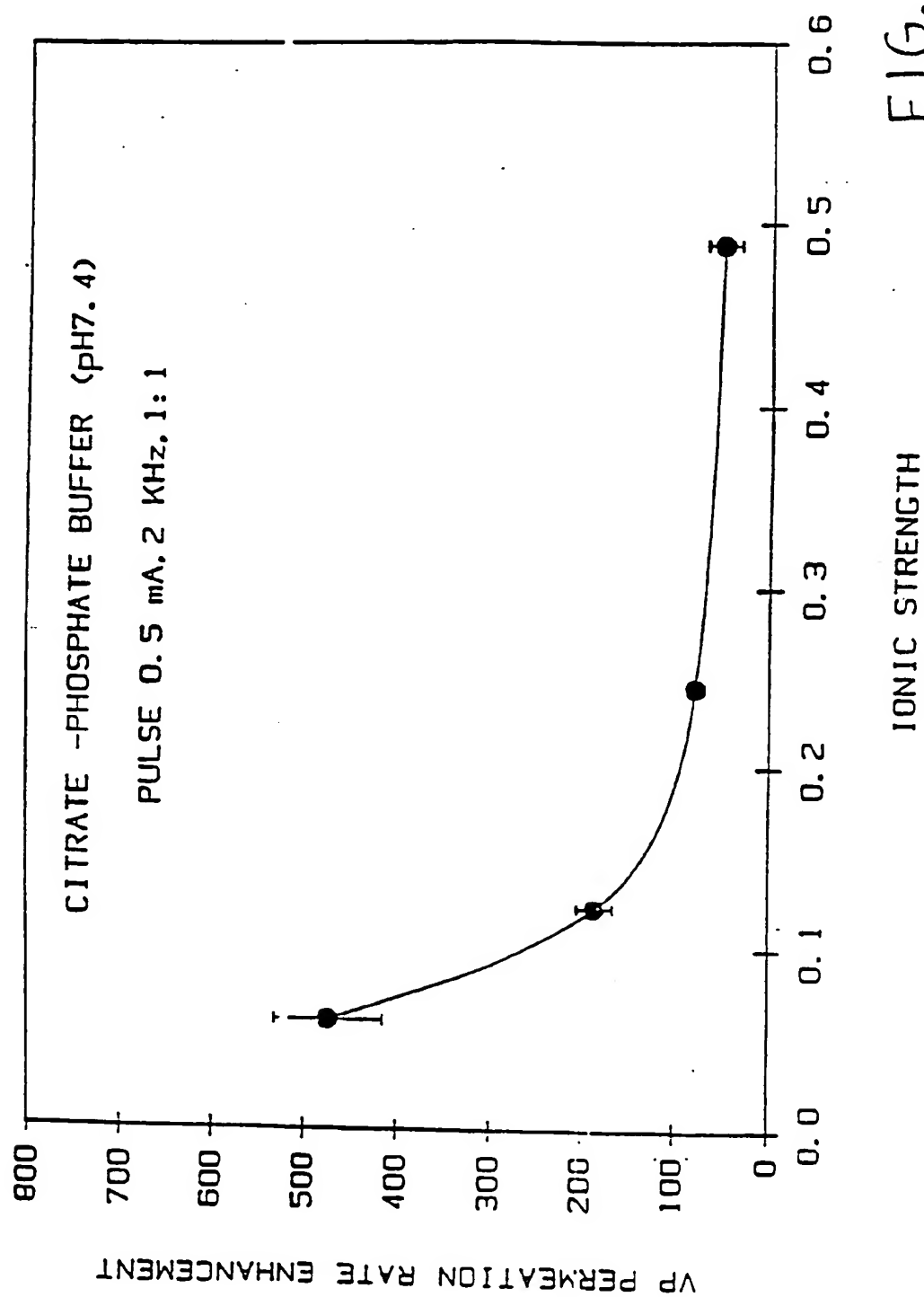


FIG. 29

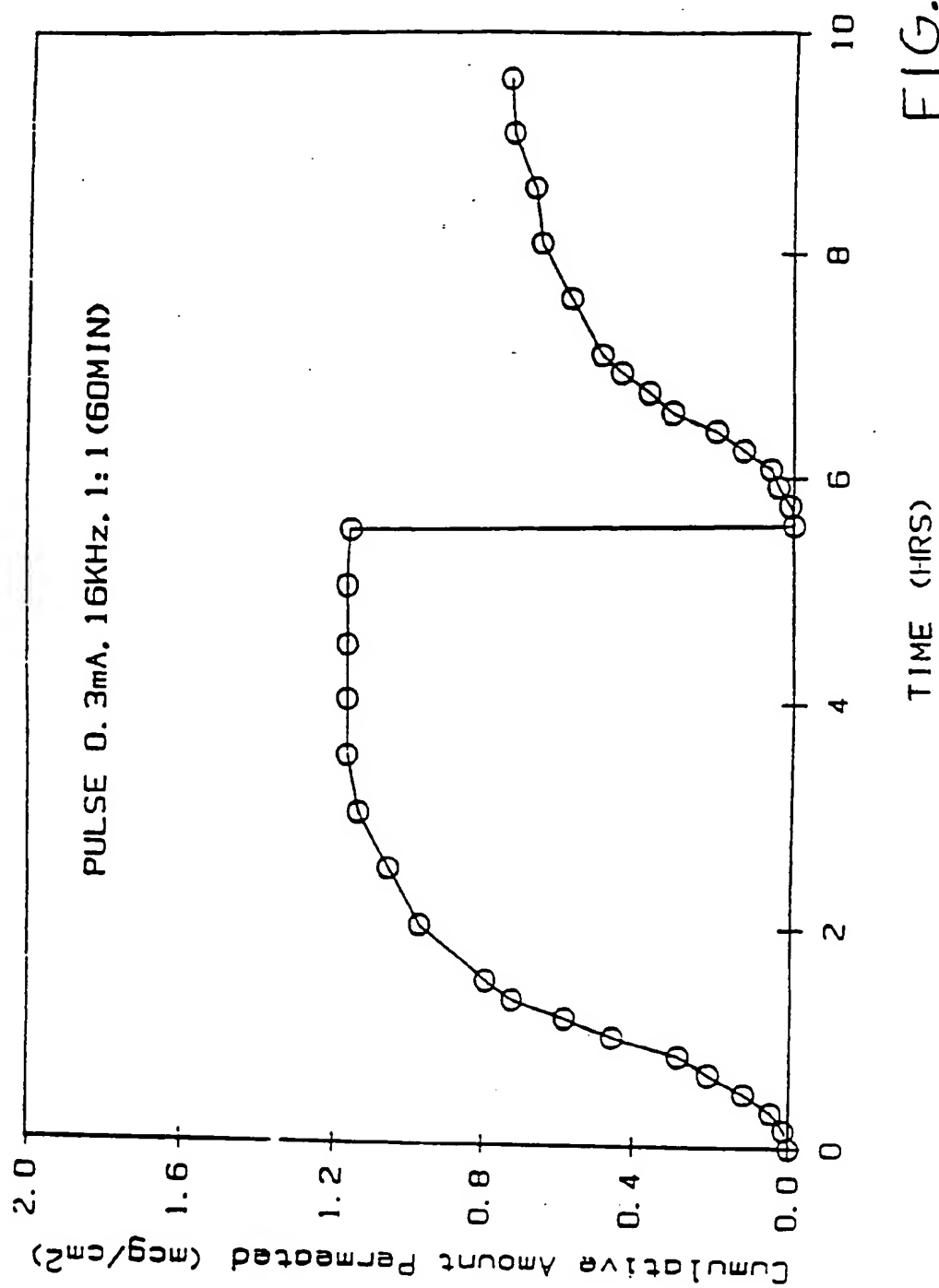


FIG. 30

INTERNATIONAL SEARCH REPORT

PCT/US92/07221

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61N1/30

US CL :604/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/748,802,803

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US,A, 5,042,975 (CHEIN ET AL) 27 AUGUST 1991 See entire document	1-19
Y	US,A, 4,722,726 (SANDERSON ET AL) 02 FEBRUARY 1988 See column 7, lines 10-16	1-17
Y	WO,A, 86/07268 (SIBALIS) 18 DECEMBER 1986 See entire document	1-17
A	WO,A, 86/07269 (MCNICHOLS ET AL) 16 FEBRUARY 1988 See Abstract	1-17

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" documents which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" documents referring to an oral disclosure, use, exhibition or other means	
"P" documents published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 23 NOVEMBER 1992	Date of mailing of the international search report 31 DEC 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer <i>Andrie Raliman</i> MICHAEL RAFA
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-2214

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07221

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,931,046 (NEWMAN) 05 JUNE 1990 See Abstract	1-17
A	US,A, 5,013,293 (SIBALIS) 07 MAY 1991 See entire document	1-17
A	US,A, 5,135,479 (SIBALIS ET AL) 04 AUGUST 1992 See entire document	1-19
A	WO, A, 86/07269 (SIBALIS ET AL.) 18 DECEMBER 1986. See entire document	1-17
A	US,A, 4,942,883 (NEWMAN) 24 JULY 1990. See Abstract, Figures)	1-17